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**Evidence-based and case-based development of a meta-algorithm for guidance of primary care encounters for patients with multimorbidity**

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**Key words:** Multimorbidity, Primary Care, Guideline Development, Clinical Practice Guidelines

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**ABSTRACT**

**Objective:** Aim of the study was to develop an overarching algorithm (meta-algorithm) to structure primary care encounters of patients with multimorbidity. We used a novel case-based *and* evidence-based procedure to overcome methodological difficulties in guideline development for patients with complex care needs.

**Study design:** Systematic guideline development methodology including systematic evidence retrieval (guideline synopses), expert judgment and informal and formal consensus procedures.

**Setting:** Primary care.

**Intervention:** The meta- algorithm was developed in six steps:

1. Design of ten case vignettes of patients with multimorbidity (common, epidemiologically confirmed disease patterns and/or particularly challenging health care needs) in a multidisciplinary workshop.
2. Based on the main diagnoses a systematic guideline synopsis of evidence- and consensus-based clinical practice guidelines was prepared. The recommendations were prioritized according to clinical and psychosocial characteristics of the case vignettes.
3. Case vignettes along with the respective guideline recommendations were validated and specifically commented by an external panel of practicing general practitioners (GPs).
4. Guideline recommendations and expert comments were summarized as case specific management recommendations (N-of-one-guidelines).
5. Health care preferences of patients with multimorbidity were elicited from a systematic literature review and supplemented with information from qualitative interviews.
6. Using pattern recognition all N-of-1-guidelines were analysed to identify common decision nodes and care elements. These elements were put together to form a generic meta-algorithm.

**Results:** The resulting meta-algorithm reflects the logic of a GP encounter of a patient with multimorbidity making explicit decision situations, communication needs and priorities. It can be filled with the complex problems of individual patients and hereby offer guidance to the practitioner. Contrary to simple, symptom-oriented algorithms the meta-algorithm illustrates a superordinate process which permanently keeps the entire patient in view.

**Conclusion:** The meta-algorithm represents the back bone of the multimorbidity guideline of the German College of General Practitioners and Family Physicians.

### STRENGTHS AND LIMITATION OF THE STUDY

This is the first study to attempt a case based „bottom-up“ approach to develop a guideline for patients with multimorbidity and complex care needs in primary care.

A methodological approach consisting of quantitative and qualitative methods was used to combine research evidence, expert opinion and patients' preferences.

The meta-algorithm in its final form was formally consented by the multidisciplinary guideline group that is led by the German College of General Practice and Family Medicine (DEGAM).

For reasons of convenience the number of underlying case vignettes was limited to ten, hereby narrowing the spectrum of multimorbidity covered.

It cannot be excluded that our sample of GPs is a selection of excellence and they might not be representative for the whole sample of all practicing primary care physicians caring for multimorbid patients.

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**INTRODUCTION**

**Background**

Multimorbidity, defined as the presence of several chronic conditions in one person, is a very common phenomenon in the elderly. It is still difficult to quantify unequivocally how many people suffer from multimorbidity as there is no general consensus on the definition or measurement of multimorbidity. (1) Which conditions contribute to multimorbidity and how many of them need to be present to constitute multimorbidity are particularly controversially debated questions. The lack of a definition explains the large differences in reported prevalence figures which depend on the disease spectrum included, the setting and the data sources used, and the time period assessed. (2–5)

The consequences of multimorbidity for the patients include functional disabilities, a lower quality of life, higher mortality, higher usage of the healthcare system, and thus higher costs. (1, 6–8) The complex care needs of patients with multimorbidity present a particular challenge for the patients themselves and for their care providers. The best explored and most widely discussed care problem is polypharmacy associated with multimorbidity. This phenomenon is characterized by incalculable interactions of medications and illnesses, adverse effects or contradictory therapeutic strategies. (9, 10) Furthermore, assistive non-pharmaceutical therapies, educational interventions, self-care measures and frequent follow-ups recommended by different single disease guidelines contribute to the treatment burden of patients with multimorbidity. Patients with 12 different, daily medications and 24 daily treatment routines - as demonstrated in the frequently cited case by Boyd 2005 – are often encountered in primary care. (11)

Given the complexity of health problems in patients with multimorbidity, there is wide consensus that the concept of “patient-centered care” should guide any approach to care. (12) The central aspects of the concept include the pursuit of a biopsychosocial disease concept, the pivotal role of patients’ central values and priorities, a doctor-patient relationship shared decision-making and a coordinated approach to interdisciplinary care. (13,14)

Specifically, for the setting of general practice, Muth et al. in 2014 formulated a set of principles (“Ariadne principles”) with the intention to give guidance for primary care consultations of patients with multimorbidity. (15) The principles follow the concept of patient-centered care and address the classic responsibilities of primary care: treating current problems, treating chronic problems, clarifying and coordinating patients’ and doctors’ expectations concerning treatment planning and opportunistic healthcare promotion. (16)

### Multimorbidity in Clinical Practice Guidelines

So far, there is only one published clinical practice guideline (CPG) explicitly focussing on the care of patients with multimorbidity. (17) The guideline published by the British National Institute of Excellence (NICE) takes a wide scope by addressing all health care professionals as well as patients, their families and carers. The German primary care guideline „Multimedikation“ (Polypharmacy) addresses medication for patients with multimorbidity, but cannot depict the entire process of primary care for this particular group of patients. (18) Clinical practice guidelines for single diseases rarely address multimorbidity. (15,17,19,20) Applying the various recommendations of all applicable single disease guidelines is barely feasible and associated with a high risk for the patients due to interactions and incompatible treatments. (11)

Aside from the clinical complexity, guideline development for patients with multimorbidity bears methodological challenges. Five methodological steps are essential for the process of developing evidence-based and consensus-based clinical practice guidelines

- 1) Assembly of a representative, interdisciplinary and multi-professional guideline development group including experts, users and patients.
- 2) Identification of the clinically relevant key questions, which lead to the guidelines main recommendations.
- 3) Systematic search for the best available empirical evidence to support the recommendations.
- 4) Appraisal of the available evidence from a clinical point of view, with a focus on relevant effects in daily practice and feasibility.
- 5) Structured, reproducible and independently moderated consensus rounds to finalize recommendations. (21,22)

This classic, data- and expert-based „Top-Down“ procedure has proven to not be particularly helpful in developing a guideline for the treatment of multimorbid patients due to the above-mentioned complexity. Using chronic heart failure and 18 common comorbidities as an example Muth et al. clearly outline the various interactions between an index illness and a patient's comorbidities, disease-drug interactions, and drug-drug interactions, (247 interactions, averagely 14 per comorbidity). (23) All of these would need to be considered during the systematic evidence review in the Top-Down guideline development procedure. The implementation of such a procedure for multimorbidity does not seem feasible, especially without focussing on a particular index illness.

**OBJECTIVE**

Against this background we elaborated and tested a “bottom-up” procedure to develop an overarching algorithm to guide a primary care encounter of a patient with multimorbidity. This algorithm is intended to be the centerpiece of an evidence- and consensus-based clinical practice guideline “Multimorbidity” (work in progress), created under the supervision of the German College of General Practitioners and Family Physicians (DEGAM). [<http://www.awmf.org/leitlinien/detail/anmeldung/1/II/053-047.html>] The multidisciplinary guideline panel comprised GPs, geriatricians, gerontologists, psychologists and health scientists with expertise in evidence-based medicine and guideline development.

**METHODS**

**General approach**

The „bottom-up“ procedure for guideline development is based on case vignettes of multimorbid patients. For every case vignette, individual management recommendations are generated, using standard guideline development methodology (problem identification/ formulation of key questions, evidence search and analysis, contextualization, consensus-finding). As in the „N-of-one-trials“ (scientific studies with only one participant) (24), the resulting recommendations are designated as „N-of-one-guidelines“. Using a qualitative synthesis of the N-of-one-guidelines a generic meta-algorithm is created that reflects management considerations for patients with multimorbidity in primary care. Figure 1 outlines the methodological steps and groups participating in the development process. The process was coordinated and largely realized by the Guideline Working Group which consisted of three general practitioners and three experts in guideline development methodology.

Figure 1

In detail, six methodical steps were followed to develop the meta-algorithm for the management of patients with multimorbidity in primary care:

**Development of Case Vignettes**

Ten Case vignettes of prototypic patients with multimorbidity consulting their GP were constructed in a single day workshop with 20 interdisciplinary (GPs, methodologists, including the Guideline Working Group) participants (Workshop Group). We chose the number of ten vignettes in order to be able to depict the most frequently seen multimorbidity patterns and disease combinations and be able to reflect particularly problematic combinations by the GPs. Disease combinations for two thirds of the vignettes were taken from epidemiological research: typical multimorbidity patterns (cardiovascular/metabolic; anxiety/depression/somatic disorders/pain-oriented morbidity; neuropsychiatric illnesses) reported in the Multicare Study (25) and frequently encountered disease combinations published by van den Bussche et al., 2011 (26). Disease combinations for one third of the



vignettes were derived from particularly difficult cases of multimorbidity presented by the participating general practitioners. Information on the clinical and psychosocial context of each case was collected based on the experience of the task force participants.

Each case vignette contained information on:

- Demographic information (Age, Gender, Occupation),
- Key information from the patient's medical history,
- Reason for consultation, main complaints/ health problem, and symptoms;
- Diagnoses which constitute the patient's „Multimorbidity“,
- Psychosocial context (e.g. marital status, housing situation etc.),
- Results of current examinations (clinical examinations or blood work),
- Medications (name, dosage, application form, prescription data),
- Psychosocial status.

### **Evidence search and analysis**

The evidence base for the management recommendations for each case vignette was derived from published evidence-based and consented clinical practice guidelines. For each case vignette a guideline synopsis was prepared including recommendations from guidelines that address the diagnoses that constitute multimorbidity in the respective vignette. For this purpose, in May 2013 the National Guideline Databases of the Association of Scientific Medical Societies (AWMF) and of the Agency for Quality in Medicine (AQuMed) were searched using the main diagnoses as search terms. Guidelines were included if they contained a systematic work-up of the research evidence. Outdated guidelines were excluded. In a first step, all guideline recommendations that applied to the main diagnoses of the case vignettes and that addressed aspects of long-term care of chronic illnesses were extracted by the scientific staff of the guideline working group. Recommendations referring to diagnostic procedures or emergency treatments were not considered. In a second step, for each case vignette the relevant guideline recommendations were identified and prioritized in a modified Delphi procedure by the clinical members of the guideline working group. Recommendations that seemed applicable - taking into consideration demographics, main ailments, psychosocial context, current medication and any additional information to the patient's current life situation - were added to the case vignettes.

**Adding clinical expertise**

All case vignettes and guideline recommendations were clinically validated by practicing general practitioners (GP expert panel). The GPs were recruited from the server list of an E-Mail-based discussion forum led and used by about 700 practicing primary care experts from all over Germany for professional exchange. The members of the server list were asked, if they were interested in participating in a research project pertaining to the healthcare of multimorbid patients. All interested physicians received 10 electronic documents containing the case vignettes, a summary of the guideline recommendations and a questionnaire. The questionnaire consisted of three open questions: 1) the necessity to avert life threatening conditions, 2) the definition of management goals and 3) relevant lifestyle and psychosocial factors to be taken into consideration. Additionally, GPs were asked whether they referred to the guideline recommendations contained in the case vignettes when answering the questions. Participants were offered a compensation of 100 €.

**Developing N-of-one-guidelines**

In a next step, the primary care process for each case vignette - based on guideline recommendations and clinical judgement - was displayed as an algorithmic graph (N-of-one-guideline). Each N-of-one-guideline sets off with the reason for the patient's current consultation. The key questions guiding the care process are generated from the case vignettes with their heterogeneous multimorbidity constellations and psychosocial contexts. The recommendations referring to the key questions are derived from the external evidence (guideline recommendations) and the clinical experts' comments. All N-of-one-guidelines were finalized in an informal consensus procedure within the guideline working group.

**Bringing in the patient's perspective**

Taking the values and preferences of the affected patient group into consideration is an essential step in guideline development. (21) In order to clarify the preferences and values of patients with multimorbidity regarding their health care two approaches were taken: 1) a systematic review of qualitative and quantitative studies and 2) qualitative interviews with 15 multimorbid patients sampled from the Multicare cohort study. (27)

For the systematic literature review Medline and Embase were searched via OVID, starting from inception until March 2015. To be included into the review, publications had to contain qualitative or quantitative information elicited from patients with multimorbidity regarding their preferences and valuations in health care. Methodological quality of the qualitative and quantitative studies was checked using criteria according to Giacomini and Cook, 2000 (28) for qualitative research and a modified Checklist of the Scottish Intercollegiate Guideline Network (29) for quantitative research. Information

from the quantitative studies was extracted into Excel-sheets and summarized qualitatively, hereby identifying relevant categories and subcategories. Information from the qualitative materials was sorted into the same categories and integrated into the summaries. If necessary, new categories were defined.

For the qualitative interviews the patients were matched to the case vignettes as closely as possible (for age, gender, and comorbidities). The interview questions were sorted according to the rundown of a practice consultation and the content analysis was based on the categories identified by the literature analysis (doctor-patient relationship, communication, therapeutic goals, subjective needs and framework conditions).

### **Synthesis of the Meta-Algorithm**

The final product, the generic meta-algorithm to guide primary care consultations of patients with multimorbidity was derived from the 10 N-of-one guidelines in an informal qualitative synthesis procedure. All N-of-one guidelines were reviewed with the goal of identifying common key questions, decision processes, necessary information resources, health care consequences, patient preferences and context considerations ("pattern recognition"). Common elements and interconnections were reformulated in a generalized way (not related to a particular patient) and put together to create an algorithm that structures a primary care consultation of a patient with multimorbidity. The final version of the meta-algorithm was consented in a nominal group process by the multidisciplinary guideline development group that is led by the German College of General Practitioners and Family Physicians (DEGAM).

## **RESULTS**

### **Case Vignettes of patients with multimorbidity**

Ten case vignettes were established within the one-day workshop by the multidisciplinary working group. Seven vignettes were based on epidemiologically confirmed disease patterns (25,26) and three vignettes are based on real patients with highly complex multimorbidity reported by the participating GPs (see table 1). In these cases, multimorbidity is constituted not only by clearly defined diseases but also by symptoms such as fatigue or gait disturbance. Age and psychosocial background of all the vignettes was contributed by the GPs who reflected situations likely to complicate medical care, self-management and/or communication.

Table 1: Overview of case vignettes

Demography	Psychosocial Context	Diagnoses
Epidemiologically confirmed disease patterns (25)		
91 years male	His wife suffered a stroke, the couple lives secluded	Depression, dementia, coronary heart disease (+ urinary incontinence and hearing loss)
66 years female	Retired, no further information	Chronic back pain, osteoporosis, headaches
82 years female	Immigrated, speaks no German	Chronic heart failure, chronic kidney failure, low blood pressure
76 years male	Lives alone, ex-wife cares for him, speech problems	High blood pressure, high cholesterol, stroke, peripheral arterial disease, combined mitral valve defect
Most frequently encountered disease combinations (26)		
82 years male	Widowed, lives alone, daughter visits every four weeks	High blood pressure, atrial fibrillation, depression
60 years male	Dock worker, shift work, smoker	High blood pressure, coronary artery disease, chronic back pain
66 years female	Retired, lives alone, no further information	High blood pressure, high cholesterol, chronic back pain, type II diabetes mellitus, polymyalgia rheumatica with arteritis temporalis, osteoporosis
Highly complex real cases, reported by participating GPs		
55 years female	Immigrated, familial problems, doesn't speak German well	High blood pressure type II diabetes mellitus, metabolic syndrome
80 years male	Retired, no further information	High blood pressure, high cholesterol, atrial fibrillation, chronic heart failure, diabetes mellitus with kidney failure and cerebral microangiopathy, coronary heart disease, multi-causal gait disturbance, sleep apnea
84 years female,	Lives alone, ambulatory care gives medications	Atrial fibrillation, heart failure, dementia, fatigue

Evidence search and analysis

The guideline search found 27 German-language, up-to-date, evidence- and consensus-based clinical practice guidelines addressing diagnoses and symptoms that constitute multimorbidity in the case vignettes. The number of guidelines to be considered per case vignette varied between two and 22. From these guidelines between 59 and 320 (average 138) recommendations with potential relevance for a respective case vignette were extracted. These data extractions were distilled into a case specific guideline synopsis not exceeding two pages. The guideline synopses were added to the case vignette.

Adding clinical expertise

Out of the GP discussion forum 18 GPs were interested in contributing to the project. They received the 10 case vignettes and guideline synopses along with the questionnaires. Completed documents were finally returned from seven participants (three female and four male GPs). The answers of the GP expert panel to the open questions complemented the guideline recommendations by putting an explicit focus

on the cases' psychosocial, cultural, and familial background. Especially upholding the patients' autonomy was assessed as a primary goal for the management of patients with multimorbidity. The GP expert panel stated that they considered the recommendations from the guideline synopses when answering the three main questions but rated them as only partially helpful.

### Developing N-of-one-guidelines

The case vignettes themselves, the case-based guideline synopses, and the clinical evaluation by primary care experts formed the basis for the algorithmic display of primary care processes for each case vignette. In total, ten algorithms were created that depict the cognitive and decision-making processes GPs and patients work through during a consultation. Figure 2 gives one example.

Figure 2: Case-specific algorithm (N-of-one-guideline)

All ten case-specific algorithms served as intermediate steps for the development of the generic "meta-algorithm" (Figure 3).

### Patient's Perspective

In the literature analysis nine relevant research projects were identified and analyzed (three quantitative studies and six qualitative studies). (30–39) Their results were merged with the results of the qualitative interviews as described above.

Multimorbid patients want to be seen and treated as individuals and want to participate in decision-making. Patients expect their GP to display honesty and a certain amount of authority, in combination with supplying sufficient information and demonstrating openness for alternative approaches to care. At the same time, respect for patients' psychosocial background and involvement of the patients' family and friends were highly valued. Formal aspects that contribute to a good doctor-patient relationship were named: sufficient time for the consultation and the embedding of a practice into a health care network that facilitates access to specialist care as well as to the non-physician therapeutic professions (e.g. physiotherapy). Among the therapeutic goals patients prioritized the ability to lead an autonomous life very high. From their point of view cognitive functioning and mobility are pivotal for autonomy, followed by other functional outcomes. The importance of continuous care was repeatedly mentioned, including means of quickly reacting to health changes or deterioration. Patients with multimorbidity furthermore expressed their preparedness to actively work on achieving care goals together with their physicians (Mundt R, Dissertation Medical Faculty of Hamburg University, in progress).

Preferences and values expressed by patients were considered as modifying components during the process of establishing the meta-algorithm.

**Synthesis of the Meta-Algorithm**

Review of the 10 N-of-one-guidelines identified a number of common elements: Every vignette sets out with a reason for the current encounter. Since GPs typically provide long-term care to their patients and also take on a coordinating role, the reason for the current encounter is viewed against the background of the patient’s long-term medical history, the so called “shared medical history”. The shared medical history consists of factual information on established diagnoses and symptoms as well as the patient’s psychosocial and familial status. Furthermore, a longstanding doctor-patient relationship contributes to development and knowledge of the patient’s values, life goals and preferences for medical care.

In all N-of-one-guidelines the key question was, whether the reason for the current encounter could be explained by facts known from the shared medical history. In case of “Yes”, a comprehensive or problem-oriented disease management with a number of precise but still generic recommendations for action results. In case of “No”, investigations whether an avertable dangerous course of disease can and needs to be avoided are required. Three main and generic foci for these investigations were identified from the n-of-one-guidelines: disease related problems, adverse drug reactions (or interactions) and an impending loss of autonomy. Again, a number of precise but generic recommendations for action were derived from the N-of-one guidelines.

Figure 3 displays the meta-algorithm as a summary of generic considerations derived from 10 case-vignettes of patients with multimorbidity in a GP encounter. In the N-of-one-guidelines the key question could not always be answered with a clear-cut “Yes” or “No”. Thus, a meta-algorithm must allow to swap from the Yes-pathway of actions to the No-pathway and *vice versa* (green arrows in Fig.3).

Figure 3: Meta-algorithm to guide care for patients with multimorbidity in general practice

**DISCUSSION**

We lined out the development of a case-based *and* evidence-based meta-algorithm to guide management of patients with multimorbidity in general practice.

The algorithm sets out with a multimorbid patient presenting with an arbitrary reason for encounter. From this starting point the cognitive processes that structure the complex consultation situation are displayed. Consideration of the patients’ preferences, values and life goals stands in the center of the algorithm and prompts shared decision making, if desired. Priority setting for either disease management or exclusion of an avoidable dangerous course is determined by the answer to one single key question. Both possible pathways are completed by generic recommendations of medical and social aspects to be covered, possible diagnostic, therapeutic and management steps to be taken and information resources to be used. The whole process is embedded in the typical GP setting with a longstanding patient-doctor relationship as the basis for a “shared medical history”. On the whole, the

meta-algorithm encompasses the main criteria for patient-centered care. (14,40,41) The meta-algorithm was distilled from ten evidence- and consensus-based N-of-one-guidelines dealing with the GP management of ten patients with heterogeneous multimorbidity (case-vignettes). The ten case vignettes were constructed to represent the most frequently encountered disease combinations as well as particularly challenging complex situations presented by practicing GPs. The N-of-one-guidelines were developed by the guideline working group, a panel of GPs and methodologists.

As a whole, the meta-algorithm reflects the logic of a GP encounter of a patient with multimorbidity making explicit aspects to consider, decision situations, communication needs and priorities. It can be filled with the complex problems of individual patients and hereby offer guidance to the individual practitioner. Contrary to simple, symptom-oriented algorithms the “meta-algorithm” illustrates a superordinate process which permanently keeps in view the entire patient. The decision-making processes are primarily guided by the reason for encounter, not by specific diagnoses or combinations of diagnoses. Naturally, avoiding an avertable, dangerous course of disease is one priority task for GP-care – provided it is compatible with the individual patient’s values and preferences. Especially the aspect of avoiding loss of autonomy and maintaining independence (in the sense of the patients’ ability to lead their own life) has gained new priority as could be read from the N-of-one-guidelines and the information regarding patients’ preferences. This goal may - in individual cases - even supersede solely disease-oriented guideline-based management decisions. Still, disease specific, evidence- and guideline-based recommendations play a pivotal role in disease management if embedded in the holistic care process.

The meta-algorithm in its final form was consented by the multidisciplinary guideline group that is led by the German Society of General Practice and Family Medicine (DEGAM).

### **Strengths and weaknesses of the methodological approach**

To our knowledge this is the first study attempting a bottom-up approach based on case-vignettes of real patients to develop an overarching algorithm for the management of patients with multimorbidity. We are aware that ten patients cannot be representative for all multimorbid patients in German general practices. For practical reasons, we restricted our work to 10 patient vignettes which at least can be designated as patients causing typical situations. Seven out of ten case vignettes obtained common disease combinations from two German epidemiological studies. (25,26) Three further case vignettes standing for particular challenging patients were developed from real cases presented by the participating GPs in the workshop. As another strength we regard the development of the N-of-one guidelines, because it followed a standard guideline development methodology for evidence- and consensus based clinical practice guidelines.



To make sure that the recommendations in the N-of-one-guidelines are evidence-based a comprehensive search for German evidence- and consensus-based guidelines was performed. Since all retrieved guidelines were of accredited high-quality (S3-Standard, according AWMF) further quality assessment was waived. (42) Prioritisation of recommendations within the development of the N-of-one guidelines was reached by consensus within the guideline working group.

For clinical validation of the cases and guideline recommendations an external GP expert panel was recruited via an email discussion forum. This sample is probably a positive selection since GPs participating in this forum have an above-average interest in improving primary care.

To assess the patients' preferences and values regarding their GP care a literature review as well as qualitative interviews were conducted. The literature search for the review was purposefully kept very specific by using "multimorbidity" as the main search term because we intended to include research that perceives "multimorbidity" as a unique entity instead of comorbidities accompanying a specific index disease. The fact, that the results from the qualitative interviews of patients with multimorbidity fitted well with the results from the literature analysis made us confident that we actually captured the main aspects of the patient perspective.

The meta-algorithm is going to form the centerpiece of the multimorbidity guideline of the DEGAM and has been consented in a formal consensus process for this purpose. In the guideline document the algorithm will be embedded in concrete evidence- and/or consensus-based recommendations concerning communication, management and coordination of care and infrastructural context.

**Comparison with the literature**

Among clinicians but also in the research community there is consensus that patients with multimorbidity and their multifold healthcare needs pose a major challenge to primary care physicians who are often overwhelmed by the complexity of problems. (43–45) Furthermore, there is agreement, that following the recommendations of every applicable clinical practice guideline for single disorders is neither feasible nor reasonable, taking into account the resulting treatment burden and numerous possible adverse interaction effects. (11,46,47) Still, so far there is only one clinical practice guideline dealing explicitly with the management of patients with multimorbidity: the guideline "Multimorbidity: clinical assessment and management" issued by the British National Institute for Health and Care (NICE).(17) The guideline was developed by use of the standard "top-down" approach to guideline development and is based on extensive literature analyses. The NICE guideline addresses not only primary care providers but all health care professionals, including both generalists and specialists. Our meta-algorithm and the NICE guideline do not contradict but complement each other: The meta-algorithm from a holistic perspective guides clinical reasoning for every GP encounter. Medical and



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3 psychosocial information from the shared medical history as well as patients' preferences, values and  
4 life goals communicated in a longstanding doctor – patient relationship back-up and guide priority  
5 setting in every new encounter. The meta-algorithm offers guidance to GPs to steer through complex  
6 clinical situations and identifying high priority problems while, at the same time, not losing complexity  
7 out of sight. The NICE guideline offers a large number of detailed recommendations while lacking the  
8 structure of clinical reasoning for primary care. The latter may be due to the fact, that the NICE guideline  
9 is not confined to primary care but addresses all participants in health care as well as patients, their  
10 relatives and carers.

11  
12 Explicitly from the perspective of primary care Muth et al. present the "Ariadne principles" resulting  
13 from an expert workshop and two extensive discussion and feedback rounds among GPs and other  
14 experts for multimorbidity from six countries in North America, Europe and Australia. The principles  
15 reflect the core elements of an ongoing counseling process for patients with multimorbidity. (15) The  
16 elements of the ariadne principles are also found in our meta-algorithm – clarifying interactions maybe  
17 part of accompanying disease management or part of investigating the avoidability of a dangerous  
18 disease course; respect for patient preferences and the mutual agreement of treatment goals are basic  
19 principles for any doctor – patient interaction at the various decision points of the algorithm. The main  
20 difference between the two concepts is that the meta-algorithm structures one specific consultation.  
21 The reason for the encounter determines priorities for the current consultation, while other aspects are  
22 posteriorised and maybe postponed to the next encounter. In this way, the meta-algorithm helps to  
23 keep a holistic view on the care of patients with multimorbidity and at the same time prevents  
24 overloading the current consultation session.

25  
26 Yet another approach is currently being tested in a pragmatic randomized controlled trial. The 3D study  
27 is testing the effectiveness of a novel approach to GP-management of patients with multimorbidity  
28 compared to usual care. The intervention is based on a conceptual framework incorporating the patient-  
29 centered care model and aims at improving patients' quality of life, reducing burden of illness and  
30 treatment and improving patients' care experience. To foster implementation of the intervention GPs  
31 receive specific training and incentives. End of the trial is scheduled for May 2017  
32 (<http://www.isrctn.com/ISRCTN06180958>). (48) The intervention of the 3D study has some overlaps  
33 with the meta-algorithm, especially the emphasis of continuity of care, the co-ordinated holistic review  
34 (instead of disease-focussed review) and the focus on patients' priorities and needs, quality of life and  
35 function and disease management. 3D furthermore focusses on detection of depression which is not  
36 explicitly addressed in the meta-algorithm.

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To prepare implementation of the meta-algorithm it will be embedded into the clinical practice guideline “Multimorbidity” of the German College of General Practitioners and Family Physicians. The guideline itself will be pilot tested and implemented subsequently.

**Conclusion**

The case-based and evidence-based meta-algorithm presented here provides guidance to handle multimorbidity in primary care. It incorporates the principles of patient-centered care. The bottom-up development based on n-of-one-guidelines recurred on research evidence as well as on GPs expertise. In turn, applying the meta-algorithm will enable in individualized evidence-based care. Implementation and testing of the meta-algorithm as a part of a clinical practice guideline will be the next steps.

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#### Footnotes

Cathleen Muche-Borowski (CMB) AND Dagmar Lühmann (DL) contributed equally.

**Contributors:** Martin Scherer (MS) was responsible for conceptual design of the case-based guideline development. IS contributed the epidemiological basis for the case vignettes. All authors contributed to the development of the case vignettes. Hans-Otto Wagner (HOW) and MS contributed clinical expertise. CMB and DL were responsible for the guideline synopsis. HOW, CMB and DL synthesized the N-of-1-guidelines. Rebekka Mundt (RM) performed literature analysis and interviews for patient preferences. All authors contributed to the compilation of the meta-algorithms. CMB and DL drafted manuscript. The final version of the paper has been reviewed and approved by all authors, including the DEGAM guideline group.

**Ethical considerations:** The Multicare cohort study was approved by the Ethics Committee of the Medical Association of Hamburg (approval no. 2881) on 8.11.2013. All participants gave a written, informed consent to participate in the study.

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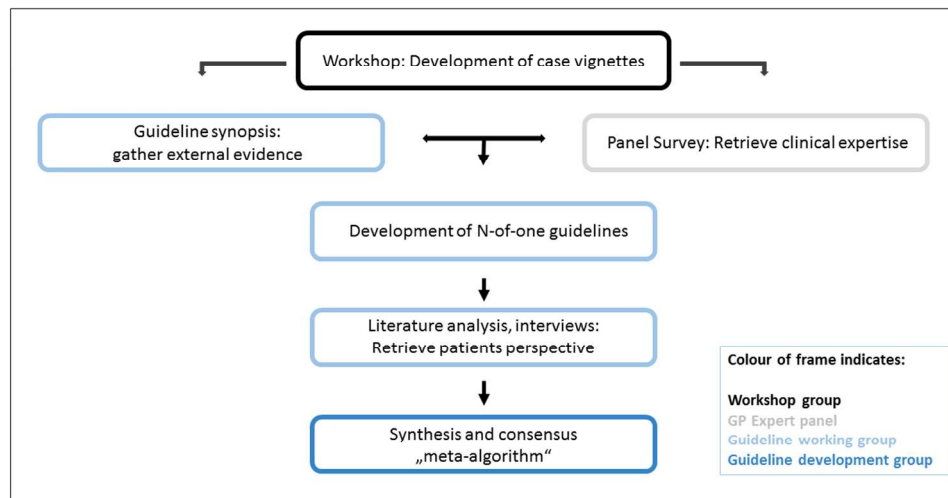
**FIGURES (LEGENDS)**

Figure 1: Methodological steps to develop a „Meta-Algorithm“ for the management of patients with multimorbidity

Figure 2: Case-specific algorithm (N-of-one-guideline): The 91-year old patient with multimorbidity presents to his family physician accompanied by his daughter. The reason for encounter is: the patient doesn’t speak anymore. Against the background of established diagnosis the GP has to decide whether the new symptom is explained by the known diagnoses. If so, progress will be made towards improved disease management. If not, exclusion of an avoidable dangerous course will be prioritised.

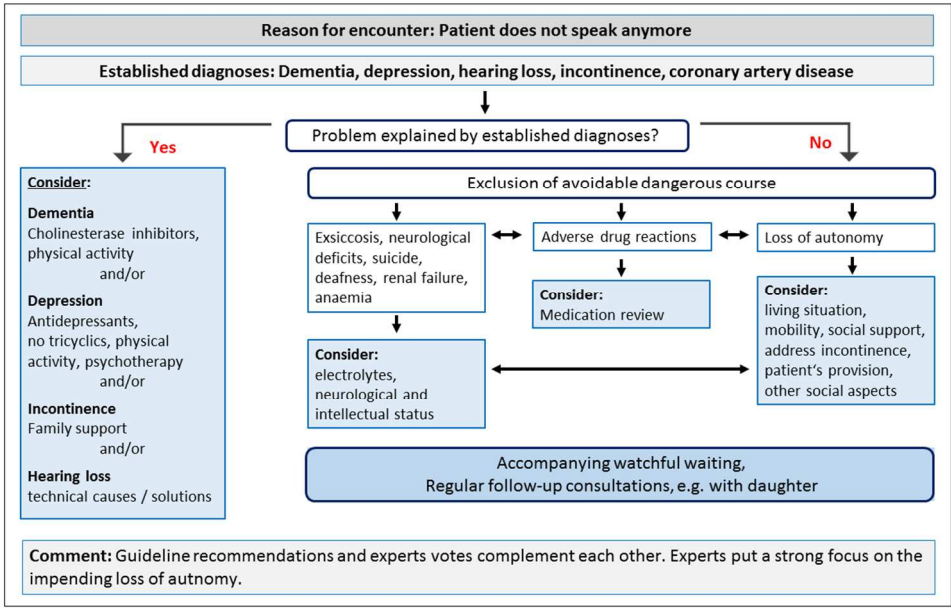
Figure 3: „Meta-Algorithm“ to guide care for patients with multimorbidity in general practice





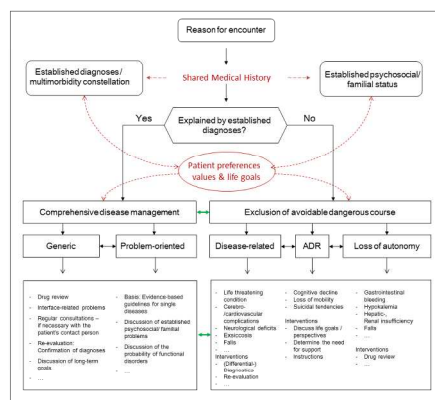
Methodological steps to develop a „Meta-Algorithm“ for the management of patients with multimorbidity

338x190mm (96 x 96 DPI)



Case-specific algorithm (N-of-one-guideline): The 91-year old patient with multimorbidity presents to his family physician accompanied by his daughter. The reason for encounter is: the patient doesn't speak anymore. Against the background of established diagnosis the GP has to decide whether the new symptom is explained by the known diagnoses. If so, progress will be made towards improved disease management. If not, exclusion of an avoidable dangerous course will be prioritised.

338x250mm (96 x 96 DPI)



„Meta-Algorithm“ to guide care for patients with multimorbidity in general practice

600x450mm (96 x 96 DPI)

# BMJ Open

## Developing of a meta-algorithm for guiding primary care encounters for patients with multimorbidity using evidence-based and case-based guideline development methodology

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<b>Primary Subject Heading</b>:	General practice / Family practice
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Keywords:	Multimorbidity, Guideline Development, Clinical Practice Guidelines

SCHOLARONE™  
Manuscripts

**Developing of a meta-algorithm for guiding primary care encounters for patients with multimorbidity using evidence-based and case-based guideline development methodology**

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**Key words:** Multimorbidity, Primary Care, Guideline Development, Clinical Practice Guidelines

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**ABSTRACT**

**Objective:** the study aimed to develop a comprehensive algorithm (meta-algorithm) for primary care encounters of patients with multimorbidity. We used a novel, case-based *and* evidence-based procedure to overcome methodological difficulties in guideline development for patients with complex care needs.

**Study design:** Systematic guideline development methodology including systematic evidence retrieval (guideline synopses), expert opinions and informal and formal consensus procedures.

**Setting:** Primary care.

**Intervention:** The meta- algorithm was developed in six steps:

1. Designing ten case vignettes of patients with multimorbidity (common, epidemiologically confirmed disease patterns and/or particularly challenging health care needs) in a multidisciplinary workshop.
2. Based on the main diagnoses a systematic guideline synopsis of evidence- and consensus-based clinical practice guidelines was prepared. The recommendations were prioritized according to the clinical and psychosocial characteristics of the case vignettes.
3. Case vignettes along with the respective guideline recommendations were validated and specifically commented on by an external panel of practicing general practitioners (GPs).
4. Guideline recommendations and experts' opinions were summarized as case specific management recommendations (N-of-one-guidelines).
5. Health care preferences of patients with multimorbidity were elicited from a systematic literature review and supplemented with information from qualitative interviews.
6. All N-of-1-guidelines were analysed using pattern recognition to identify common decision nodes and care elements. These elements were put together to form a generic meta-algorithm.

**Results:** The resulting meta-algorithm reflects the logic of a GP's encounter of a patient with multimorbidity regarding decision-making situations, communication needs and priorities. It can be filled with the complex problems of individual patients and hereby offer guidance to the practitioner. Contrary to simple, symptom-oriented algorithms the meta-algorithm illustrates a superordinate process which permanently keeps the entire patient in view.

**Conclusion:** The meta-algorithm represents the back bone of the multimorbidity guideline of the German College of General Practitioners and Family Physicians. This article presents solely the development phase, the meta-algorithm needs to be piloted before it can be implemented.

### STRENGTHS AND LIMITATION OF THE STUDY

This is the first study to attempt a case-based "bottom-up" approach to developing a guideline for patients with multimorbidity and complex care needs in primary care.

A methodological approach consisting of quantitative and qualitative methods was used to combine research evidence, experts' opinions and patients' preferences.

The meta-algorithm in its final form was formally consented by the multidisciplinary guideline group that is led by the German College of General Practice and Family Medicine (DEGAM).

For reasons of convenience the number of underlying case vignettes was limited to ten, hereby narrowing the covered spectrum of multimorbidity.

It cannot be excluded that our sample of GPs is a selection of excellence and they might not be representative for the whole sample of all practicing primary care physicians caring for multimorbid patients.



INTRODUCTION

Background

Multimorbidity, defined as the presence of several chronic conditions in one person, is a very common phenomenon in the elderly. It is still difficult to quantify unequivocally how many people suffer from multimorbidity as there is no general consensus on the definition or measurement of multimorbidity. (1) Which conditions contribute to multimorbidity and how many of them need to be present to constitute multimorbidity are particularly controversially debated questions. The lack of a definition explains the large differences in reported prevalence figures which depend on the disease spectrum included, the setting and the data sources used, and the time period assessed. (2–5)

The consequences of multimorbidity for the patients include functional disabilities, a lower quality of life, higher mortality, higher usage of the healthcare system, and thus higher costs. (1, 6–8) The complex care needs of patients with multimorbidity present a particular challenge for the patients themselves and for their care providers. The best explored and most widely discussed care problem is the polypharmacy associated with multimorbidity. This phenomenon is characterized by incalculable interactions of medications and illnesses, adverse effects or contradictory therapeutic strategies. (9, 10) Furthermore, assistive non-pharmaceutical therapies, educational interventions, self-care measures and frequent follow-ups recommended by different individual disease guidelines contribute to the treatment burden of patients with multimorbidity. Patients with 12 different daily medications and 24 daily treatment routines - as demonstrated in the frequently cited case by Boyd 2005 – are often encountered in primary care. (11)

Given the complexity of health problems in patients with multimorbidity, there is wide consensus that the concept of "patient-centered care" should guide any approach to care. (12) The central aspects of the concept include the pursuit of a biopsychosocial disease concept, the pivotal role of patients' central values and priorities, a doctor-patient relationship, shared decision-making and a coordinated approach to interdisciplinary care. (13, 14)

Muth et al. in 2014 formulated a set of principles ("Ariadne principles") specifically for the general practice setting with the intention to guide primary care consultations of patients with multimorbidity. (15) The principles follow the concept of patient-centered care and address the classic responsibilities of primary care: treating current problems, treating chronic problems, clarifying and coordinating patients' and doctors' expectations concerning treatment planning and opportunistic healthcare promotion. (16)

Multimorbidity in Clinical Practice Guidelines

So far, there is only one published clinical practice guideline (CPG) explicitly focussing on the care of patients with multimorbidity. (17) The guideline published by the British National Institute of Excellence

(NICE) takes a wide scope by addressing all health care professionals as well as patients, their families and caregivers. The German primary care guideline "Multimedikation" (Polypharmacy) addresses medication for patients with multimorbidity, but cannot depict the entire primary care process for this particular group of patients. (18) Clinical practice guidelines for single diseases rarely address multimorbidity. (15, 17, 19, 20) Applying the various recommendations of all applicable single disease guidelines is barely feasible and associated with a high risk for the patients due to interactions and incompatible treatments. (11)

Aside from the clinical complexity, guideline development for patients with multimorbidity bears methodological challenges. Five methodological steps are essential for the process of developing evidence-based and consensus-based clinical practice guidelines

- 1) Assembly of a representative, interdisciplinary and multi-professional guideline development group including experts, users and patients.
- 2) Identification of the clinically relevant key questions, which lead to the guidelines' main recommendations.
- 3) Systematic search for the best available empirical evidence to support the recommendations.
- 4) Appraisal of the available evidence from a clinical point of view, with a focus on relevant effects in daily practice and feasibility.
- 5) Structured, reproducible and independently moderated consensus rounds to finalize recommendations. (21, 22)

This classic, data- and expert-based "Top-Down" procedure has not proven particularly helpful in developing a guideline for the treatment of multimorbid patients due to the above-mentioned complexity. Using chronic heart failure and 18 common comorbidities as an example, Muth et al. clearly outlined the various interactions between an index illness and a patient's comorbidities, disease-drug interactions, and drug-drug interactions, (247 interactions, averagely 14 per comorbidity). (23) All of these would need to be considered during the systematic evidence review in the Top-Down guideline development procedure. The implementation of such a procedure for multimorbidity does not seem feasible, especially without focussing on a particular index illness.

#### OBJECTIVE

Against this background, we elaborated and tested a "bottom-up" procedure to develop a comprehensive algorithm to guide a primary care encounter of a patient with multimorbidity. The algorithm aims to give primary care encounters of patients with multimorbidity a structure. It is

intended to support the setting of priorities in patients with complex care needs. The algorithm is intended to be the centerpiece of an evidence- and consensus-based clinical practice guideline "Multimorbidity" (work in progress), created under the supervision of the German College of General Practitioners and Family Physicians (DEGAM). [<http://www.awmf.org/leitlinien/detail/anmeldung/1/II/053-047.html>] The multidisciplinary guideline panel was comprised of GPs, geriatricians, gerontologists, psychologists and health scientists with expertise in evidence-based medicine and guideline development.

**METHODS**

**General approach**

The "bottom-up" procedure for guideline development is based on case vignettes of multimorbid patients. Individual management recommendations were generated for each case vignette, using standard guideline development methodology (problem identification/ formulation of key questions, evidence search and analysis, contextualization, consensus-finding). As in the "N-of-one-trials" (scientific studies with only one participant) (24), the resulting recommendations were considered "N-of-one-guidelines". Using a qualitative synthesis of the N-of-one-guidelines, a generic meta-algorithm was created that reflects management considerations for patients with multimorbidity in primary care. Figure 1 outlines the methodological steps and groups participating in the development process. The process was coordinated and largely realized by the Guideline Working Group which consisted of three general practitioners and three experts in guideline development methodology.

Figure 1

In detail, six methodical steps were followed to develop the meta-algorithm for the management of patients with multimorbidity in primary care:

**Development of Case Vignettes**

Ten Case vignettes of prototypic patients with multimorbidity consulting their GP were constructed in a single day workshop with 20 interdisciplinary (GPs, methodologists, including the Guideline Working Group) participants (Workshop Group). We chose ten vignettes in order to be able to depict the most frequently seen multimorbidity patterns and disease combinations and be able to reflect particularly problematic combinations as seen by the GPs. Disease combinations for two thirds of the vignettes were taken from epidemiological research: typical multimorbidity patterns (cardiovascular/metabolic; anxiety/depression/somatic disorders/pain-oriented morbidity; neuropsychiatric illnesses) reported in the Multicare Study (25) and frequently encountered disease combinations published by van den Bussche et al., 2011 (26). Disease combinations for one third of the vignettes were derived from particularly difficult cases of multimorbidity presented by the participating general practitioners.

Information on the clinical and psychosocial context of each case was collected based on the experience of the task force participants.

Each case vignette contained information on:

- Demographics (Age, Gender, Occupation),
- The patient's medical history,
- Reason for consultation, main complaints/ health problem, and symptoms;
- Diagnoses which constitute the patient's "Multimorbidity",
- Psychosocial context (e.g. marital status, housing situation etc.),
- Results of current examinations (clinical examinations or blood work),
- Medications (name, dosage, application form, prescription data),
- Psychosocial status.

### **Evidence search and analysis**

The evidence base used in creating the management recommendations for each case vignette was derived from published evidence-based and consented clinical practice guidelines. A guideline synopsis was prepared for each case vignette including recommendations from guidelines that address the diagnoses that constitute multimorbidity in the respective vignette. In May 2013 the National Guideline Databases of the Association of Scientific Medical Societies (AWMF) and of the Agency for Quality in Medicine (AQuMed) were searched using the main diagnoses as search terms to create this base of evidence. Guidelines were included if they were up-to-date and contained a systematic work-up of the research evidence (see web appendix 1). In a first step, all guideline recommendations that applied to the main diagnoses of the case vignettes and that addressed aspects of long-term care of chronic illnesses were extracted by the scientific staff of the guideline working group. Recommendations referring to diagnostic procedures or emergency treatments were not considered. In a second step, the relevant guideline recommendations were identified and prioritized for each case vignette in a modified Delphi procedure by the clinical members of the guideline working group. Recommendations that seemed applicable - taking into consideration demographics, main ailments, psychosocial context, current medication and any additional information to the patient's current life situation - were added to the case vignettes.

**Adding clinical expertise**

All case vignettes and guideline recommendations were clinically validated by practicing general practitioners (GP panel). The GPs were recruited from the server list of an E-Mail-based professional discussion forum led and used by about 700 practicing primary care physicians from all over Germany. The members of the server's list were asked, if they were interested in participating in a research project pertaining to the healthcare of multimorbid patients. All interested physicians received 10 electronic documents containing the case vignettes, a summary of the guideline recommendations and a questionnaire. The questionnaire consisted of three open-ended questions: 1) the necessity to avert life threatening conditions, 2) the definition of management goals and 3) relevant lifestyle and psychosocial factors to be taken into consideration. Additionally, GPs were asked whether they referred to the guideline recommendations contained in the case vignettes when answering the questions. Participants were offered a compensation of 100 €.

**Developing N-of-one-guidelines**

In a next step, the primary care process for each case vignette was displayed as an algorithmic graph (N-of-one-guideline) based on guideline recommendations and clinical judgement. Each N-of-one-guideline starts off with the reason for the patient's current consultation. The key questions guiding the care process are generated from the case vignettes with their heterogeneous multimorbidity constellations and psychosocial contexts. The recommendations referring to the key questions are derived from the external evidence (guideline recommendations) and the GP panel comments. All N-of-one-guidelines were finalized in an informal consensus procedure within the guideline working group.

**Bringing in the patient's perspective**

Taking the values and preferences of the affected patient group into consideration is an essential step in guideline development. (21) Two approaches were taken in order to clarify the preferences and values of patients with multimorbidity regarding their healthcare: 1) a systematic review of qualitative and quantitative studies and 2) qualitative interviews with 15 multimorbid patients sampled from the Multicare cohort study. (27) This process was part of a dissertation project (RM) which will be published separately. The main methodological aspects and results are documented in the web appendix 2.

For the systematic literature review Medline and Embase were searched via OVID, starting from inception until March 2015. In order to be included into the review, publications had to contain qualitative or quantitative information elicited from patients with multimorbidity regarding their preferences and values in health care. The methodological quality of the qualitative and quantitative studies was checked using the Giacomini and Cook's, 2000 (28) criteria for qualitative research and a modified Checklist of the Scottish Intercollegiate Guideline Network (29) for quantitative research.

Information from the quantitative studies was extracted into Excel-sheets and summarized qualitatively, hereby identifying relevant categories and subcategories. Information from the qualitative materials was sorted into the same categories and integrated into the summaries. If necessary, new categories were defined.

For the qualitative interviews the patients were matched to the case vignettes as closely as possible (for age, gender, and comorbidities). The interview questions were sorted according to the rundown of a practice consultation and the content analysis was based on the categories identified by the literature analysis (doctor-patient relationship, communication, therapeutic goals, subjective needs and framework conditions).

### **Synthesis of the Meta-Algorithm**

The final product, the generic meta-algorithm to guide primary care consultations of patients with multimorbidity was derived from the 10 N-of-one guidelines in an informal, qualitative, synthesis procedure. All N-of-one guidelines were reviewed with the goal of identifying common key questions, decision-making processes, necessary information resources, health care consequences, patient preferences and context considerations ("pattern recognition"). Common elements and interconnections were reformulated, generalized (not related to a particular patient) and combined to create an algorithm that structures a primary care consultation of a patient with multimorbidity. The final version of the meta-algorithm was consented in a nominal group process by the multidisciplinary guideline development group that is led by the German College of General Practitioners and Family Physicians (DEGAM).

## **RESULTS**

### **Case Vignettes of patients with multimorbidity**

Ten case vignettes were established within the one-day workshop by the multidisciplinary working group. Seven vignettes were based on epidemiologically confirmed disease patterns (25, 26) and three vignettes are based on real patients with highly complex multimorbidity reported by the participating GPs (see table 1). In these cases, multimorbidity is constituted not only by clearly defined diseases but also by symptoms such as fatigue or gait disturbance. The patients' ages and psychosocial backgrounds in all vignettes were contributed by the GPs who reflected on situations likely to complicate medical care, self-management and/or communication.

Table 1: Overview of case vignettes

Demography	Psychosocial Context	Diagnoses
Epidemiologically confirmed disease patterns (25)		
91 years male (figure 1)	His wife suffered a stroke, the couple lives secluded	Depression, dementia, coronary heart disease (+ urinary incontinence and hearing loss)
66 years female (web appendix 3)	Retired, no further information	Chronic back pain, osteoporosis, headaches
82 years female (web appendix 4)	Immigrated, speaks no German	Chronic heart failure, chronic kidney failure, low blood pressure
55 years female (web appendix 5)	Immigrated, familial problems, doesn't speak German well	High blood pressure, type II diabetes mellitus, metabolic syndrome
Most frequently encountered disease combinations (26)		
82 years male (web appendix 6)	Widowed, lives alone, daughter visits every four weeks	High blood pressure, atrial fibrillation, depression
60 years male (web appendix 7)	Dock worker, shift work, smoker	High blood pressure, coronary artery disease, chronic back pain
84 years female (web appendix 8)	Lives alone, ambulatory care gives medications	Atrial fibrillation, heart failure, dementia, fatigue
Highly complex real cases, reported by participating GPs		
76 years male (web appendix 9)	Lives alone, ex-wife cares for him, speech problems	High blood pressure, high cholesterol, stroke, peripheral arterial disease, combined mitral valve defect
80 years male (web appendix 10)	Retired, no further information	High blood pressure, high cholesterol, atrial fibrillation, chronic heart failure, diabetes mellitus with kidney failure and cerebral microangiopathy, coronary heart disease, multi-causal gait disturbance, sleep apnea
66 years female (web appendix 11)	Retired, lives alone, no further information	High blood pressure, high cholesterol, chronic back pain, type II diabetes mellitus, polymyalgia rheumatica with arteritis temporalis, osteoporosis

Evidence search and analysis

The guideline search found 27 German (language), up-to-date, evidence- and consensus-based clinical practice guidelines addressing diagnoses and symptoms that constitute multimorbidity in the case vignettes. The number of guidelines to be considered per case vignette varied between two and 22.



Between 59 and 320 (average 138) of the guideline recommendations with potential relevance for a respective case vignette were extracted. These data extractions were distilled into a case specific guideline synopsis not exceeding two pages. The guideline synopses were added to the case vignette.

### **Adding clinical expertise**

18 GPs of the discussion forum were interested in contributing to the project. They received the 10 case vignettes and guideline synopses along with the questionnaires. Completed documents were finally returned from seven participants (three female and four male GPs). The GP panel's answers to the open questions complemented the guideline recommendations by putting an explicit focus on the cases' psychosocial, cultural, and familial backgrounds. Upholding the patients' autonomy was considered a particularly primary goal for managing patients with multimorbidity. The GP panel stated that they considered the recommendations from the guideline synopses when answering the three main questions but rated them as only partially helpful.

### **Developing N-of-one-guidelines**

The case vignettes themselves, the case-based guideline synopses, and the clinical evaluation by primary care physicians formed the basis for the algorithmic display of primary care processes for each case vignette. In total, ten algorithms (see web appendix 3-11) were created that depict the cognitive and decision-making processes which GPs and patients work through during a consultation. Figure 2 gives one example.

Figure 2: Case-specific algorithm (N-of-one-guideline)

All ten case-specific algorithms served as intermediate steps for the development of the generic "meta-algorithm" (Figure 3).

### **Patient's Perspective**

Nine relevant research projects were identified and analyzed in the literature analysis (six qualitative studies and three quantitative studies). (30–39) Their results were merged with the results of the qualitative interviews as described above.

Patients' preferences, as expressed in the qualitative studies, were grouped into five main categories: doctor-patient-relationship, subjective health care needs, communication, organizational framework of health care and treatment goals. The categories were not independent of each other. The organizational context of health care (such as health insurance, access, availability of providers) forms the basis for all other categories. Communication enables the build-up of a doctor-patient-relationship as well as the expression of needs and the formulation of health-care goals. The results from the quantitative studies as well as the interviews (40) were fitted into these categories.



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Multimorbid patients want to be seen and treated as individuals and want to participate in the decision-making process regarding their healthcare. Patients expect their GPs to display honesty and a certain amount of authority, in combination with supplying sufficient information and demonstrating openness for alternative approaches to care. At the same time, respect for patients' psychosocial backgrounds and involvement of the patients' families and friends were highly valued. Formal aspects that contribute to a good doctor-patient relationship were named: sufficient time for the consultation and the embedding of a practice into a health care network that facilitates access to specialist care as well as to the non-physician therapeutic professions (e.g. physiotherapy). Among the therapeutic goals patients prioritized the ability to lead an autonomous life. From their point of view cognitive functioning and mobility are pivotal for autonomy, followed by other functional outcomes. The importance of continuous care was repeatedly mentioned, including means of quickly reacting to health changes or deterioration. Patients with multimorbidity furthermore expressed their preparedness to actively work on achieving care goals together with their physicians (Mundt R, Dissertation Medical Faculty of Hamburg University, in progress).

Preferences and values expressed by patients were considered modifying components during the process of establishing the meta-algorithm.

**Synthesis of the Meta-Algorithm**

Review of the 10 N-of-one-guidelines identified a number of common elements: Every vignette sets out with a reason for the current encounter. Since GPs typically provide long-term care to their patients and also take on a coordinating role, the reason for the current encounter is viewed against the background of the patient's long-term medical history, the so called "shared medical history". The shared medical history consists of the factual information on established diagnoses and symptoms as well as of the patient's psychosocial and familial status. Furthermore, a longstanding doctor-patient relationship contributes to the development and knowledge of the patient's values, life goals and preferences for medical care.

In all N-of-one-guidelines the key question was, whether the reason for the current encounter could be explained by facts known from the shared medical history. "Yes" results in a comprehensive or problem-oriented disease management with a number of precise but still generic recommendations for action. In case of "No", investigations on whether an avertable dangerous course of disease can and needs to be avoided are required. Three main and generic foci for these investigations were identified from the n-of-one-guidelines: disease-related problems, adverse drug reactions (or interactions) and an impending loss of autonomy. Again, a number of precise but generic recommendations for action were derived from the N-of-one guidelines.

Figure 3 displays the meta-algorithm as a summary of generic considerations derived from 10 case-vignettes of patients with multimorbidity in a GP encounter. In the N-of-one-guidelines the key question could not always be answered with a clear-cut "Yes" or "No". Thus, a meta-algorithm must allow to swap from the Yes-pathway of actions to the No-pathway and *vice versa* (green arrows in Fig. 3).

Figure 3: Meta-algorithm to guide the care of patients with multimorbidity in general practice

## DISCUSSION

We outlined the development of a case-based *and* evidence-based meta-algorithm to guide the management of patients with multimorbidity in general practices.

The algorithm sets out with a multimorbid patient presenting with an arbitrary reason for encounter. From this starting point the cognitive processes that structure the complex consultation situation are displayed. The consideration of patients' preferences, values and life goals stands in the center of the algorithm and prompts shared decision-making, if desired. Priority setting for either disease management or exclusion of an avoidable dangerous course is determined by the answer to one single key question. Both possible pathways are completed by generic recommendations of medical and social aspects to be covered, possible diagnostic, therapeutic and management steps to be taken and information resources to be used. The whole process is embedded in the typical GP setting with a longstanding patient-doctor relationship as the basis for a "shared medical history". On the whole, the meta-algorithm encompasses the main criteria for patient-centered care. (14, 41, 42) The meta-algorithm was distilled from ten evidence- and consensus-based N-of-one-guidelines dealing with the GP management of ten patients with heterogeneous multimorbidity (case-vignettes). The ten case vignettes were constructed to represent the most frequently encountered disease combinations as well as particularly challenging complex situations presented by practicing GPs. The N-of-one-guidelines were developed by the guideline working group, a panel of GPs and methodologists.

As a whole, the meta-algorithm reflects the logic of a GP encounter of a patient with multimorbidity regarding explicit aspects to consider, decision situations, and communication needs and priorities. It can be filled with the complex problems of individual patients and hereby offer guidance to the individual practitioner. Contrary to simple, symptom-oriented algorithms, the "meta-algorithm" illustrates a superordinate process which permanently considers all aspects of a patient. The decision-making processes are primarily guided by the reason for encounter, not by specific diagnoses or combinations of diagnoses. Naturally, avoiding an avertable, dangerous course of disease is a main priority in GP-care – provided it is compatible with the individual patient's values and preferences. Especially avoiding the loss of autonomy and maintaining independence (in the sense of the patients' abilities to lead their own lives) has gained new priority as could be gathered from the N-of-one-

guidelines and the information regarding patients' preferences. This goal may - in individual cases - even supersede solely disease-oriented guideline-based management decisions. Still, disease specific, evidence- and guideline-based recommendations play a pivotal role in disease management, if embedded in the holistic care process.

The meta-algorithm in its final form was consented by the multidisciplinary guideline group that is led by the German Society of General Practice and Family Medicine (DEGAM).

**Strengths and weaknesses of the methodological approach**

To our knowledge this is the first study attempting a bottom-up approach based on case-vignettes of real patients to develop a comprehensive algorithm for managing of patients with multimorbidity. We are aware that ten patients cannot be representative for all multimorbid patients in German general practices. For practical reasons, we restricted our work to 10 patient vignettes which can at least be considered typical patients/situations. Seven out of ten case vignettes obtained common disease combinations from two German epidemiological studies. (25, 26) Three further case vignettes representing particularly challenging patients were developed from real cases presented by the participating GPs in the workshop. As another strength we regard the development of the N-of-one guidelines, because it followed a standard guideline development methodology for evidence- and consensus based clinical practice guidelines.

To make sure that the recommendations in the N-of-one-guidelines are evidence-based a comprehensive search for German evidence- and consensus-based guidelines was performed. Further quality assessment was waived since all retrieved guidelines were of accredited a high-quality (S3-Standard, according AWMF). (43) The prioritisation of recommendations within the development of the N-of-one guidelines was reached by consensus within the guideline working group.

An external GP panel was recruited via an email discussion forum to clinically validate the cases. This small sample of seven GPs is likely a positive selection since participants in this forum have an above-average interest in improving primary care. This disadvantage has to be accounted for in the pilot study, which needs to include a larger and more representative sample of GPs in Germany.

A literature review as well as qualitative interviews were conducted in order to assess the patients' preferences and values regarding the care received through their GPs. The literature search for the review was purposefully kept very specific by using "multimorbidity" as the main search term because we intended to include research that perceives "multimorbidity" as a unique entity instead of comorbidities accompanying a specific index disease. The fact, that the results from the qualitative

interviews of patients with multimorbidity corresponded well with the results from the literature analysis made us confident that we actually captured the main aspects of the patient perspective.

The meta-algorithm is going to form the centerpiece of the multimorbidity guideline of the DEGAM and has been consented in a formal consensus process for this purpose. The algorithm will be embedded in concrete evidence- and/or consensus-based recommendations concerning communication, management and coordination of care and infrastructural context in the guideline document. The meta-algorithm could, in itself, be useful in structuring primary care encounters outside Germany since it does not refer to a specific infrastructural context.

### Comparison with the literature

Among clinicians but also in the research community there is a consensus that patients with multimorbidity and their multifold healthcare needs pose a major challenge to primary care physicians who are often overwhelmed by the complexity of problems. (44–46) Furthermore, it is agreed, that following the recommendations of every applicable clinical practice guideline for single disorders is neither feasible nor reasonable, taking into account the resulting treatment burden and numerous possible adverse interaction effects. (11, 47, 48) Still, the evidence on the effectiveness of interventions to improve the outcomes of patients with multimorbidity is rather limited. A recent Cochrane Review (49) reported the effectiveness of organizational (twelve RCTs) and patient-oriented (six RCTs) interventions to improve the outcomes of patients with multimorbidity in primary care and community settings. The authors conclude that there is a good amount of uncertainty remaining as concerns the effectiveness of interventions due to the relatively small number of studies available to date and their mixed results. An improvement of the evidence base is to be expected though since the authors identified 15 ongoing trials. Interventions like the meta-algorithm, which would be classified as a professional intervention (50) were not addressed in the review. Still, one of the conclusions the authors of the Cochrane Review came to was that, in order to achieve sustainability, interventions have to integrate with the existing health care system. A requirement that is met by this meta-algorithm.

So far there is still only one clinical practice guideline dealing explicitly with the management of patients with multimorbidity: the guideline "Multimorbidity: clinical assessment and management" issued by the British National Institute for Health and Care (NICE). (17) The guideline was developed via the standard "top-down" approach to guideline development and is based on extensive literature analyses. The NICE guideline addresses not only primary care providers but all health care professionals, including both generalists and specialists. Our meta-algorithm and the NICE guideline do not contradict but complement each other: The meta-algorithm guides clinical reasoning for every GP encounter from a holistic perspective. Medical and psychosocial information from the shared medical history as well as

patients’ preferences, values and life goals communicated in a longstanding doctor – patient relationship back-up and guide priority setting in every new encounter. The meta-algorithm offers guidance to GPs in steering through complex clinical situations and identifying high priority problems while, at the same time, not losing sight of their complexity. The NICE guideline offers a large number of detailed recommendations while lacking the clinical reasoning structure in primary care. The latter may be due to the fact, that the NICE guideline is not confined to primary care but addresses all participants in health care as well as patients, their relatives and caregivers.

Muth et al. present the "Ariadne principles" resulting from an expert workshop and two extensive discussion and feedback rounds among GPs and other experts for multimorbidity in primary care from six countries in North America, Europe and Australia. The principles reflect the core elements of an ongoing counseling process for patients with multimorbidity. (15) The elements of the ariadne principles are also found in our meta-algorithm – clarifying interactions may be part of accompanying disease management or part of investigating the avoidability of a dangerous disease course; respecting patient preferences and the mutual agreement on treatment goals are basic principles for any doctor – patient interaction at the various decision points of the algorithm. The main difference between the two concepts is that the meta-algorithm structures one specific consultation. The reason for the encounter determines priorities for the current consultation, while other aspects are posteriorised and maybe postponed to the next encounter. In this way, the meta-algorithm helps to keep a holistic view on the care of patients with multimorbidity and at the same time prevents overloading the current consultation session.

Another intervention, which has some similarities to the proposed meta-algorithm, has been pilot-tested in an exploratory cluster randomized trial (CARE Plus study). The intervention, which is termed a “whole-system-intervention” was applied in primary care practices in Glasgow and addressed patients with multimorbidity from deprived areas. It consists of longer and structured primary care consultations, the establishment of a care plan and self-help support (CARE Approach). The exploratory trial demonstrated positive effects on some endpoints (negative well-being, quality of life) and indicated that the intervention was cost-effective. (51, 52)

Yet another approach is currently being tested in a pragmatic randomized controlled trial. The 3D study is testing the effectiveness of a novel approach to GP-management of patients with multimorbidity compared to usual care. The intervention is based on a conceptual framework incorporating the patient-centered care model and aims at improving patients’ quality of life, reducing the burden of illness and treatment and improving patients’ care experiences. GPs received specific training and incentives to foster the implementation of the intervention. The trial is scheduled to end in May 2017 [<http://www.isrctn.com/ISRCTN06180958>]. The intervention of the 3D study has some overlaps with the

meta-algorithm, especially in the emphasis on the continuity of care, the co-ordinated holistic review (instead of disease-focused review) and the focus on patients' priorities and needs, quality of life and function and disease management. 3D furthermore focusses on detecting depression which is not explicitly addressed in the meta-algorithm. (53)

To prepare the implementation of the meta-algorithm it will be embedded into the clinical practice guideline "Multimorbidity" of the German College of General Practitioners and Family Physicians. The guideline itself will be pilot tested in a sample of GP practices in northern Germany with a primary focus on feasibility and practicability. After necessary modifications are made based on the evaluation results, a quantitative evaluation is planned to investigate the process and patient outcomes. Therefore, the implementation of the meta-algorithm will ideally be complemented by the use of a classification system such as the ICPC. This system can be used to document multiple episodes of care in one patient over time. (54)

## Conclusion

The case-based and evidence-based meta-algorithm presented here provides guidance on handling multimorbidity in primary care. It incorporates the principles of patient-centered care. The bottom-up development based on n-of-one-guidelines was based on research evidence as well as on GPs' clinical expertise. In turn, applying the meta-algorithm will enable in individualized evidence-based care. The next steps will incorporate the implementation and testing of the meta-algorithm in practices as a part of a clinical practice guideline.

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**Footnotes**

Cathleen Muche-Borowski (CMB) AND Dagmar Lühmann (DL) contributed equally.

**Contributors:** Martin Scherer (MS) was responsible for conceptual design of the case-based guideline development. IS contributed the epidemiological basis for the case vignettes. All authors contributed to the development of the case vignettes. Hans-Otto Wagner (HOW) and MS contributed clinical expertise. CMB and DL were responsible for the guideline synopsis. HOW, CMB and DL synthesized the N-of-1-guidelines. Rebekka Mundt (RM) performed literature analysis and interviews for patient preferences. All authors contributed to the compilation of the meta-algorithms. CMB and DL drafted manuscript. The final version of the paper has been reviewed and approved by all authors, including the DEGAM guideline group.

**Ethical considerations:** The Multicare cohort study was approved by the Ethics Committee of the Medical Association of Hamburg (approval no. 2881) on 8.11.2013. All participants gave a written, informed consent to participate in the study.

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**Competing Interests:** All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.



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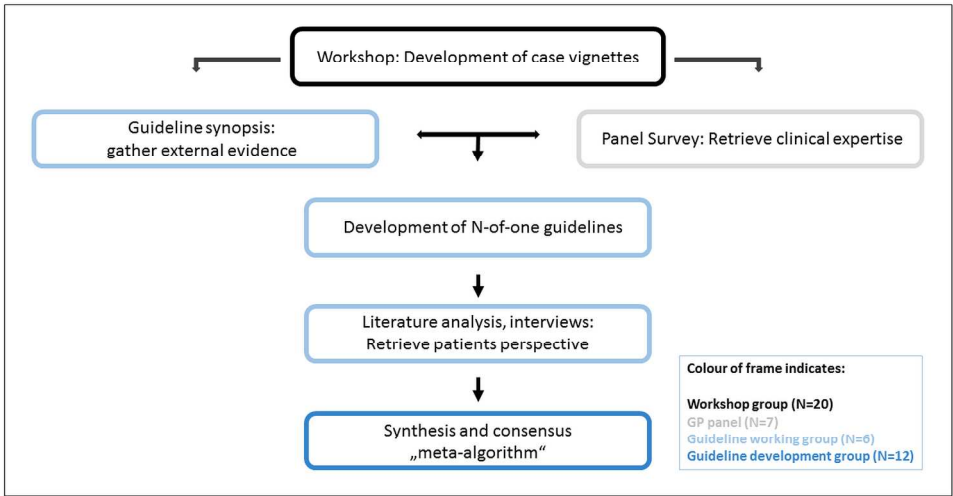
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## FIGURES (LEGENDS)

Figure 1: Methodological steps to develop a "Meta-Algorithm" for the management of patients with multimorbidity

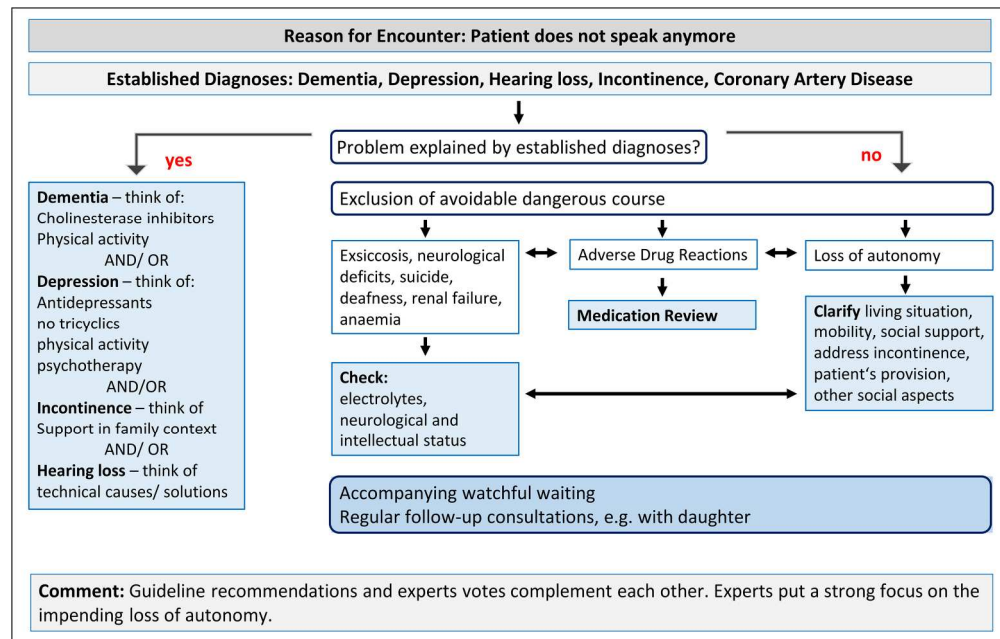
Figure 2: Case-specific algorithm (N-of-one-guideline): The 91-year old patient with multimorbidity presents to his family physician accompanied by his daughter. The reason for encounter is: the patient doesn't speak anymore. Against the background of established diagnosis the GP has to decide whether the new symptom is explained by the known diagnoses. If so, progress will be made towards improved disease management. If not, exclusion of an avoidable dangerous course will be prioritized.

Figure 3: "Meta-Algorithm" to guide care for patients with multimorbidity in general practice



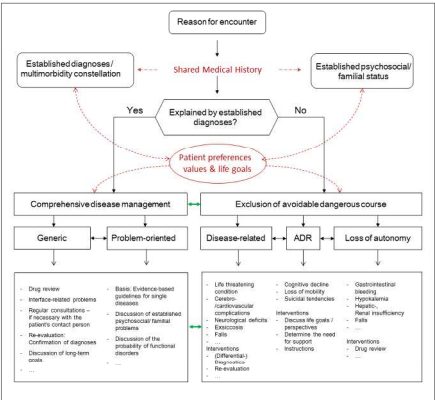
Methodological steps to develop a "Meta-Algorithm" for the management of patients with multimorbidity

338x190mm (300 x 300 DPI)



Case-specific algorithm (N-of-one-guideline): The 91-year old patient with multimorbidity presents to his family physician accompanied by his daughter. The reason for encounter is: the patient doesn't speak anymore. Against the background of established diagnosis the GP has to decide whether the new symptom is explained by the known diagnoses. If so, progress will be made towards improved disease management. If not, exclusion of an avoidable dangerous course will be prioritized.

204x130mm (300 x 300 DPI)



„Meta-Algorithm“ to guide care for patients with multimorbidity in general practice

600x450mm (96 x 96 DPI)

## Web appendix 1: Overview of included guidelines

Diagnosis	Guideline
<b>Hypertension</b>	Neue Entwicklungen in der Hochdrucktherapie 2011; Deutsche Hochdruckliga e.V. DHL und Deutsche Gesellschaft für Hypertonie und Prävention <a href="https://www.hochdruckliga.de/nachrichtendetails/items/neue-entwicklungen-in-der-hochdrucktherapie.html">https://www.hochdruckliga.de/nachrichtendetails/items/neue-entwicklungen-in-der-hochdrucktherapie.html</a>
	Leitlinien zur Behandlung der arteriellen Hypertonie 2008; Deutsche Hochdruckliga e.V. DHL - Deutsche Hypertonie Gesellschaft <a href="https://www.hochdruckliga.de/bluthochdruck-behandlung-leitlinien.html">https://www.hochdruckliga.de/bluthochdruck-behandlung-leitlinien.html</a>
<b>Atrial fibrillation</b>	Leitlinien für das Management von Vorhofflimmern 2012; Deutsche Gesellschaft für Kardiologie <a href="https://leitlinien.dgk.org/2013/pocket-leitlinien-fur-das-management-von-vorhofflimmern-fokus-update-2012/">https://leitlinien.dgk.org/2013/pocket-leitlinien-fur-das-management-von-vorhofflimmern-fokus-update-2012/</a>
	DEGAM-Leitlinie Nr. 8: Schlaganfall (Kapitel 5.2.2.2 Vorhofflimmern) 2012; Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin <a href="http://www.degam.de/degam-leitlinien-379.html">http://www.degam.de/degam-leitlinien-379.html</a>
<b>Coronary heart disease</b>	Chronische KHK 2006; Nationale VersorgungsLeitlinie <a href="http://www.awmf.org/leitlinien/detail/II/nvl-004.html">http://www.awmf.org/leitlinien/detail/II/nvl-004.html</a>
	Chronische KHK - Modul Medikamentöse Therapie 2011; Nationale VersorgungsLeitlinie <a href="http://www.awmf.org/leitlinien/detail/II/nvl-004.html">http://www.awmf.org/leitlinien/detail/II/nvl-004.html</a>
<b>Chronic heart failure</b>	Chronische Herzinsuffizienz 2012; Nationale VersorgungsLeitlinien <a href="http://www.awmf.org/leitlinien/detail/II/nvl-006.html">http://www.awmf.org/leitlinien/detail/II/nvl-006.html</a>
<b>Heart valve defect</b>	Pocket-Leitlinien: Klappenvitien im Erwachsenenalter 2007; Deutschen Gesellschaft für Kardiologie <a href="https://leitlinien.dgk.org/2007/pocket-leitlinie-klappenvitien-im-erwachsenenalter/">https://leitlinien.dgk.org/2007/pocket-leitlinie-klappenvitien-im-erwachsenenalter/</a>
	Deutsche Leitlinie zur Rehabilitation von Patienten mit Herz-Kreislaufkrankungen 2007; Deutsche Gesellschaft für Prävention und Rehabilitation von Herz-Kreislaufkrankungen e.V. <a href="http://www.dgpr.de/leitlinien-empfehlungen-positionspapiere.html">http://www.dgpr.de/leitlinien-empfehlungen-positionspapiere.html</a>
<b>Dyslipidemia</b>	Hausärztliche Leitlinie - Kardiovaskuläre Prävention 2011; Leitliniengruppe Hessen <a href="http://www.pmvforschungsguppe.de/content/03_publicationen/03_d_leitlinien.html">http://www.pmvforschungsguppe.de/content/03_publicationen/03_d_leitlinien.html</a>
<b>Type II diabetes mellitus</b>	Empfehlungen zur antihyperglykämischen Therapie des Diabetes mellitus Typ 2 2009; Arzneimittelkommission der Deutschen Ärzteschaft <a href="http://www.akdae.de/Arzneimitteltherapie/TE/A-Z/index.html">http://www.akdae.de/Arzneimitteltherapie/TE/A-Z/index.html</a>
	Nierenerkrankungen bei Diabetes im Erwachsenenalter 2010, Nationale VersorgungsLeitlinien <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html</a>
	Neuropathie bei Diabetes im Erwachsenenalter 2011; Nationale VersorgungsLeitlinien <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html</a>
	Präventions- und Behandlungsstrategien für Fußkomplikationen 2006; Nationale VersorgungsLeitlinien (aktuell in der Überarbeitung) <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html</a>
	Prävention und Therapie von Netzhautkomplikationen 2006; Nationale VersorgungsLeitlinien (aktuell in der Überarbeitung) <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html</a>
	Körperliche Aktivität und Diabetes mellitus 2008; Deutschen Diabetes-Gesellschaft



	<a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte- leitlinien.html</a>
	Evidenz-basierte Ernährungsempfehlungen zur Behandlung und Prävention des Diabetes mellitus 2005; Deutsches Diabetes-Zentrum <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-&lt;br/&gt;leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte- leitlinien.html</a>
	Diabetes – Strukturierte Schulungsprogramme 2013; Nationale VersorgungsLeitlinien <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-&lt;br/&gt;leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte- leitlinien.html</a>
<b>Dementia</b>	S3-Leitlinie Demenzen 2009; Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde und Deutsche Gesellschaft für Neurologie <a href="http://www.kompetenznetz-demenzen.de/fachpublikum/leitlinien/">http://www.kompetenznetz-demenzen.de/fachpublikum/leitlinien/</a>
	DEGAM-Leitlinie Nr. 12: Demenz 2008; Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin <a href="http://www.degam.de/degam-leitlinien-379.html">http://www.degam.de/degam-leitlinien-379.html</a>
<b>Depression</b>	S3-Leitlinie Unipolare Depression 2013; Nationale VersorgungsLeitlinie <a href="http://www.awmf.org/leitlinien/detail/II/nvl-005.html">http://www.awmf.org/leitlinien/detail/II/nvl-005.html</a>
<b>Back pain</b>	Kreuzschmerz 2011; Nationale VersorgungsLeitlinie <a href="http://www.awmf.org/leitlinien/detail/II/nvl-007.html">http://www.awmf.org/leitlinien/detail/II/nvl-007.html</a>
<b>Osteoporosis</b>	Prophylaxe, Diagnostik und Therapie der Osteoporose bei Erwachsenen 2009; Dachverbandes Osteologie (DVO) <a href="http://www.osteoporose-portal.de/arzt/DVO-LL-2010">http://www.osteoporose-portal.de/arzt/DVO-LL-2010</a>
<b>Headache</b>	Umgang mit Patienten mit nicht-spezifischen, funktionellen und somatoformen Körperbeschwerden 2012; Deutsche Gesellschaft für Psychosomatische Medizin und Ärztliche Psychotherapie e.V. und Deutsches Kollegium für Psychosomatische Medizin <a href="http://www.awmf.org/leitlinien/detail/II/051-001.html">http://www.awmf.org/leitlinien/detail/II/051-001.html</a>
<b>Polymyalgia rheumatica</b>	Ness T, Bley TA, Schmidt WA, Lamprecht P: Diagnose und Therapie der Riesenzellarteriitis. Dtsch Arztebl Int 2013; 110(21): 376–86. <a href="https://www.aerzteblatt.de/archiv/138880/Diagnose-und-Therapie-der-Riesenzellarteriitis">https://www.aerzteblatt.de/archiv/138880/Diagnose-und-Therapie-der-Riesenzellarteriitis</a>
<b>Sleep apnea</b>	Therapie der obstruktiven Schlafapnoe des Erwachsenen 2009; Dt. Ges. f. Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie <a href="https://www.hno.org/publikationen/leitlinien.html">https://www.hno.org/publikationen/leitlinien.html</a>
	S3-Leitlinie – Nicht erholsamer Schlaf/Schlafstörungen 2009; Deutsche Gesellschaft für Schlafforschung und Schlafmedizin <a href="http://www.dgsm.de/">http://www.dgsm.de/</a>

## Web appendix 2: Methodology of literature analysis on patient preferences

### Literature Search

We used a combined search strategy for qualitative and quantitative studies investigating health care preferences of patients with multimorbidity. The search strategy consisted of three modules (multimorbidity, patient preferences and study design). Within the modules the search terms were combined using the operator "OR", the three modules were combined using the operator "AND".

Table 1 App 2: Search terms and modules

multimorbidity	patient preferences	study design
multimorbid*	„patient* centered“	„focus group“
comorbid*	„patient* satisfaction“	interview
„frail elderly“	„patient* view“	survey
	„patient* perception“	„mixed method*“
	„patient* perspective“	„qualitative study“
	„patient* preference“	„qualitative research“
	expectation*	

Search strategy for Medline and Embase via Ovid (inception to March 2015):

((((((("qualitative study") OR "Qualitative Research"[Mesh]) OR "mixed method\*") OR survey) OR interview) OR "Focus Groups"[Mesh])) AND (((("Comorbidity"[Mesh]) OR multimorbid\*) OR "Frail Elderly"[Mesh])) AND (((((((("Patient Preference"[Mesh]) OR "patient\* perspective") OR "patient\* perception") OR "patient\* view") OR "patient\* satisfaction") OR "patient\* centered") OR expectation\*). The search yielded 650 hits after removal of duplicates.

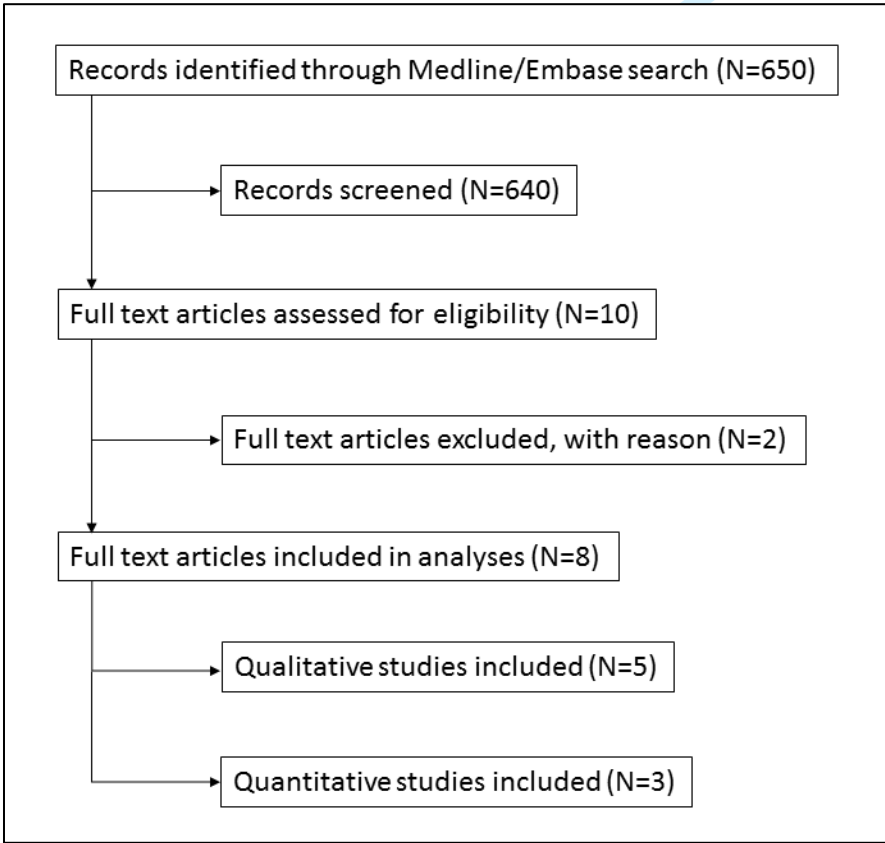
Inclusion/exclusion criteria

Table 2 App 2: In- and exclusion criteria in the literature analysis

	Inclusion criteria	Exclusion criteria
patients	patients with multimorbidity ≥ 2 diseases	studies reporting on patients with a specific index disease and comorbidities;
study objective	investigation of patients’ healthcare preferences and priorities	effectiveness studies to improve the outcomes of patients with multimorbidity
Study design - qualitative studies	any qualitative study with a transparently documented state-of- the-art methodological approach; systematic reviews of qualitative studies with a transparently documented methodological approach	studies without transparently documented state-of-the-art methodological approach; unsystematic reviews
Study design – quantitative studies	cross-sectional studies, surveys, baseline examination of prospective studies	

After removal of duplicates 650 hits remained to screened for inclusion into the review.

Figure 1 App 2: Flow Chart of literature selection



## Characteristics of included studies

Table 3 App 2: Study characteristics of included studies – Qualitative studies

1 <sup>st</sup> author, year, country	Objective	Inclusion criteria	Exclusion criteria	Participants	Methodology	Quality criteria*
Robben et al., 2011 Netherlands	Investigation of preferences for receiving information among frail elderly (and their informal care givers).	'frail elderly' over 65, defined as: more than 1 of: cognitive impairment; physical handicap; psychosocial problems; multimorbidity; polypharmacy; social isolation. (Dutch College of General Practitioners)	unable to speak (Dutch); severe hearing loss; life expectancy < 6 months; severe cognitive deficits.	f: 9 m: 2	semi-structured interviews; grounded theory	10/11
van Kempen et al., 2011 Netherlands  <i>same study as Robben et al. 2011</i>	Investigation of the needs and preferences of frail older people concerning home visits of family physicians.	'frail elderly' over 65, defined as: more than 1 of: cognitive impairment; physical handicap; psychosocial problems; multimorbidity; polypharmacy; social isolation. (Dutch College of General Practitioners)	unable to speak (Dutch); severe hearing loss; life expectancy < 6 months; severe cognitive deficits.	f: 9 m: 2	semi-structured interviews; grounded theory	10/11

1 <sup>st</sup> author, year, country	Objective	Inclusion criteria	Exclusion criteria	Participants	Methodology	Quality criteria*
Ekdahl et al., 2010 Sweden	Investigation of patients' preferences for shared decision making when admitted to hospital for an acute illness.	'frail elderly' as defined by the Swedish National Centre of Epidemiology 2001: > 75 years, > 3 hospital stays within the last 12 months, > 3 ICD-10 diagnoses	unable to speak (Swedish), substantial dementia	f: 10 m: 5	semi-structured interviews; content analysis according to Graneheim and Lundman with manifest and latent focus.	11/11
Fried et al., 2008 USA	Investigating multimorbid patients views on and knowledge about drug effects and interactions.	≥ 65 years ≥ 5 drugs 16 further criteria characterizing multimorbidity.	unable to speak (English); severe hearing loss; severe cognitive deficits.	f: 44 m: 22	13 focus groups; grounded theory	10/11
Bayliss et al., 2008 USA	Explore processes of care desired by elderly patients who have multimorbidities.	≥ 65 years at least: diabetes, depression, osteoarthritis; stratified random sample from survey respondent population; members of one HMO	n.g.	f: 13 m: 13	face-to-face, semi-structured interviews, content analysis	9/11
Noel et al., 2005 USA	To explore the collaborative care needs and preferences in primary care patients with multiple chronic illnesses.	Veterans Health Administration, primary care clinics (found by purposive sampling): ≥ diagnoses	severe cognitive impairment; uncontrolled psychiatric illness	f: 12 m: 48	focus groups, content analysis	8/11

1 <sup>st</sup> author, year, country	Objective	Inclusion criteria	Exclusion criteria	Participants	Methodology	Quality criteria*
Jerant et al., 2005	(1) to elicit perceived barriers to active self-management; and (2) to elicit perceived barriers to accessing self-management support services and resources.	convenience sample from university: (1) diagnosis of one or more of the study chronic illnesses (arthritis, asthma, COPD, CHF, depression, and DM); (2) aged 40 or older; (3) able to read at 7th grade level and speak English; (4) residing in a private home; and (5) interest in discussing chronic illness self-management. (85% had ≥ 2 chronic illnesses)	n.g.	f: 37 m:17	focus groups content analysis	10/11
f: female; m: male; n.g.: not given *criteria derived from Giacomini and Cook 2000						

Table 4 App 2: Study characteristics of included studies – quantitative studies

1 <sup>st</sup> author, year, country	Objective	Inclusion criteria	Exclusion criteria	Participants	Methodology	Quality criteria*
<b>Quantitative studies</b>						
Killiari et al., 2014 Cyprus	Investigation of prevalence of multimorbidity in Cyprus and patients' satisfaction with health care.	Patients with ≥ 2 diagnoses, 18-88 years, representative household sample, excluding institutional residents and group housings.	n.g.	f: 264 m: 201	cross-sectional study, personal interviews	3/6
Fung et al., 2008 USA	Investigate relationship between multimorbidity and patient's rating of communication.	Random sample of households from 12 communities with > 200.000 inhabitants drawn from the CTS Household Surveys national sample.	n.g.	f: 8204 m: 7505	cross-sectional study, telephone interviews	4/6
Noel et al., 2007 USA	Comparison of need for self-management-education between patients with multimorbidity and patients with single diseases.	Patients from a 'Veterans Affairs Medical Center' with at least 1 contact over the last 13 months. Either multimorbid patients (≥ 3 diagnoses) or patients with just one chronic disease	n.g.	patients with multimorbidity: n = 227 patients with single disease: n=195	cross-sectional study	5/6
f: female; m: male; n.g.: not given *criteria: participant selection; responder/ non-responder; clearly focused endpoint definition; validated questionnaires; measurement if confounding variables; documentation of missing values						

## Excluded studies with reasons

Table 5 App 2: Excluded studies

Study	Reason for exclusion
Junius-Walker et al.: Impact of a priority-setting consultation on doctor-patient agreement after a geriatric assessment: cluster randomised controlled trial in German general practices. Qual Prim Care. 2012;20(5):321-34.	Interventional study
Wrede J et al.: Complex health care decisions with older patients in general practice: patient-centeredness and prioritization in consultations following a geriatric assessment. Patient Educ Couns. 2013 Jan;90(1):54-60  <i>same study as Junius-Walker et al.</i>	Interventional study
Löffler C et al.: Optimizing polypharmacy among elderly hospital patients with chronic diseases--study protocol of the cluster randomized controlled POLITE-RCT trial. Implement Sci. 2014 Oct 6;9:151.	Study protocol



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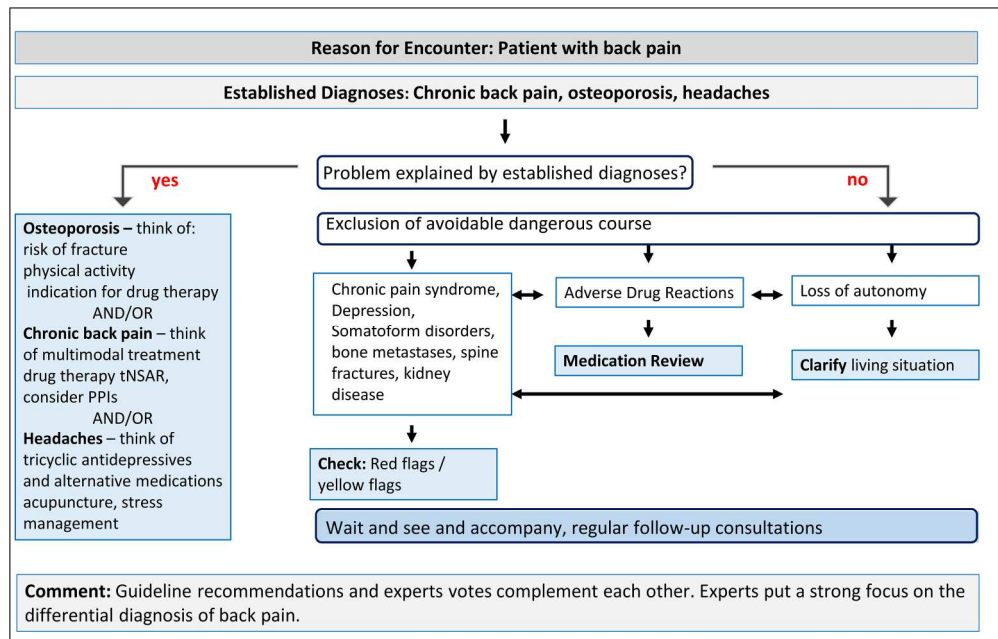
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Kiliari N, Theodosopoulou E, Papanastasiou E. Multimorbidity and unmet citizens' needs and expectations urge for reforms in the health system of Cyprus: a questionnaire survey. *JRSM Open*. 2014;5(1):2042533313515860.

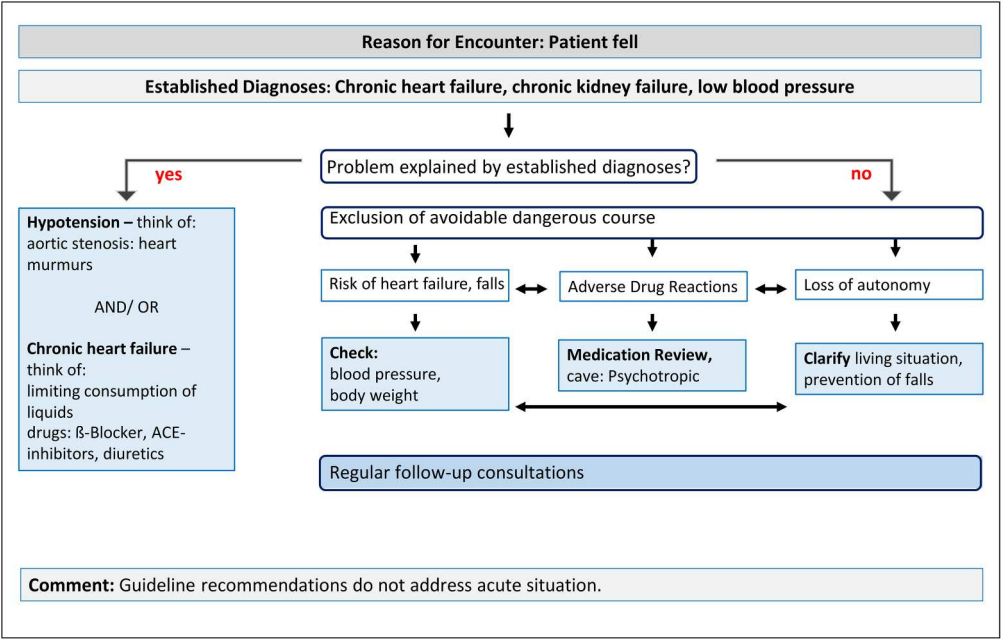
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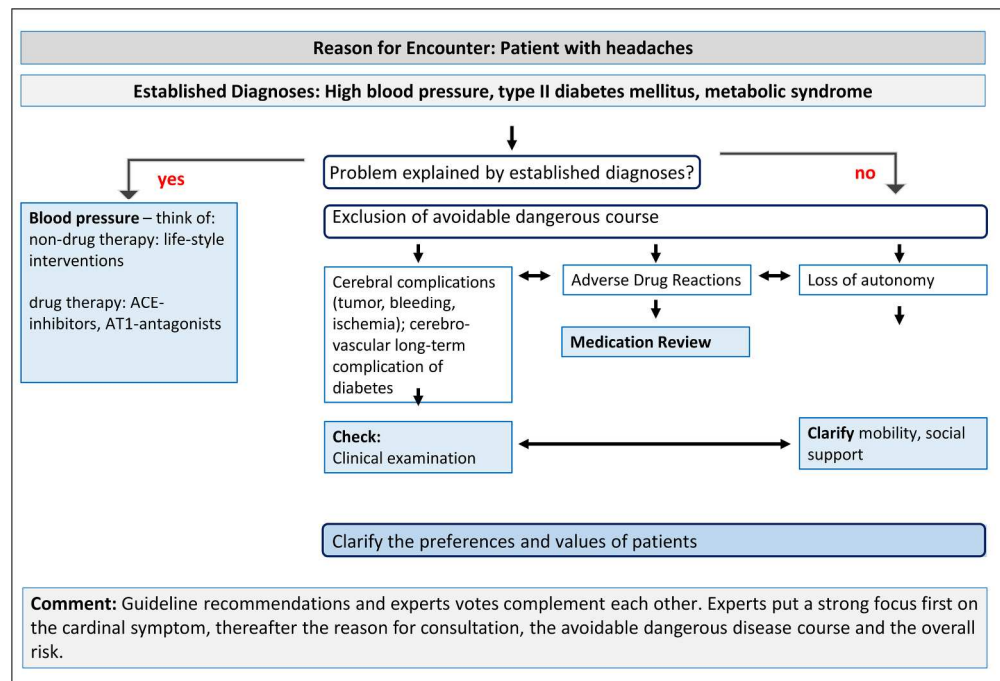
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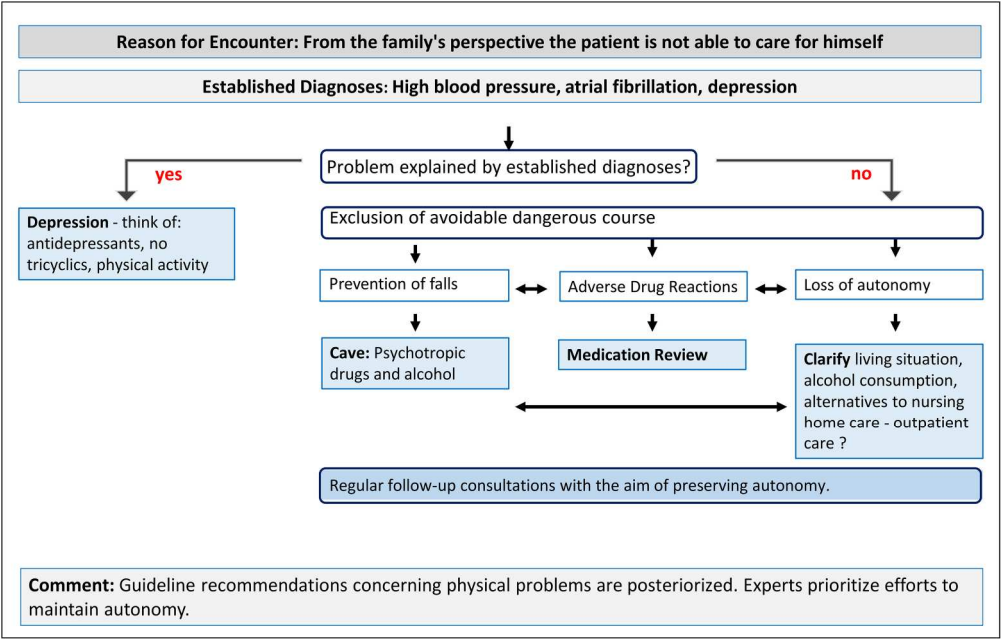
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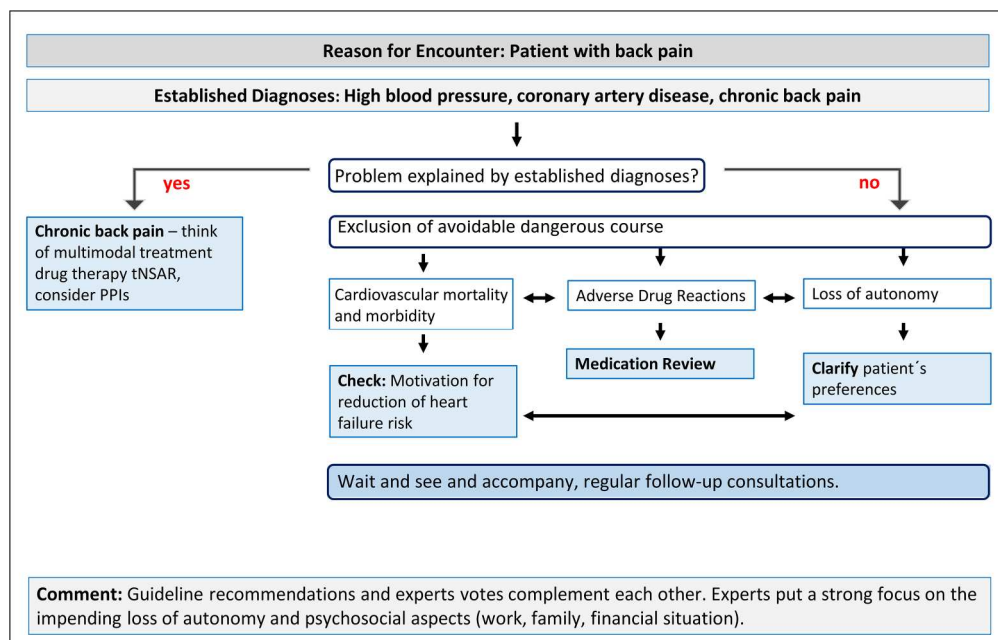
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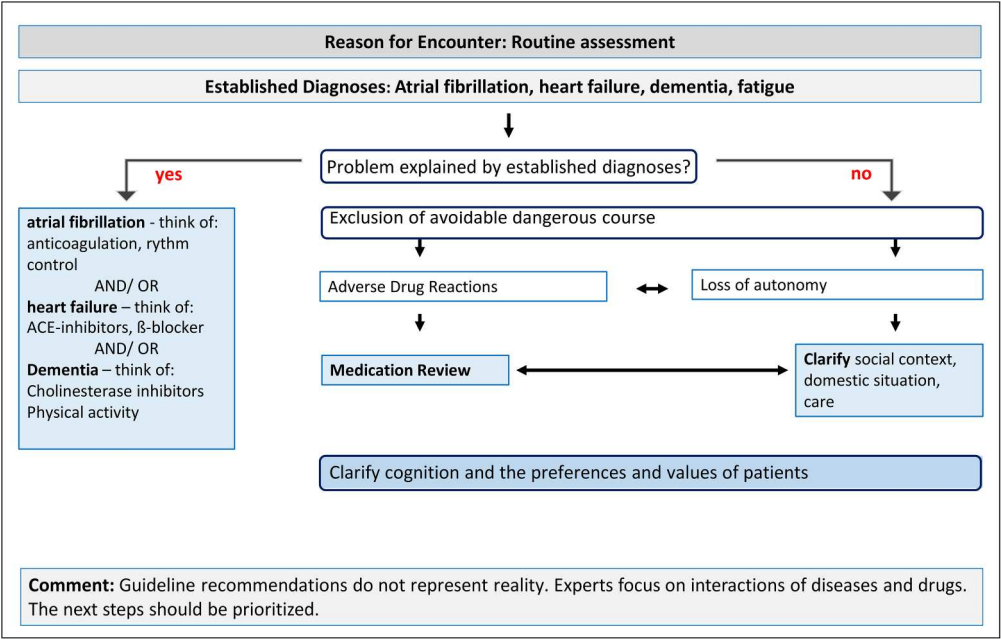
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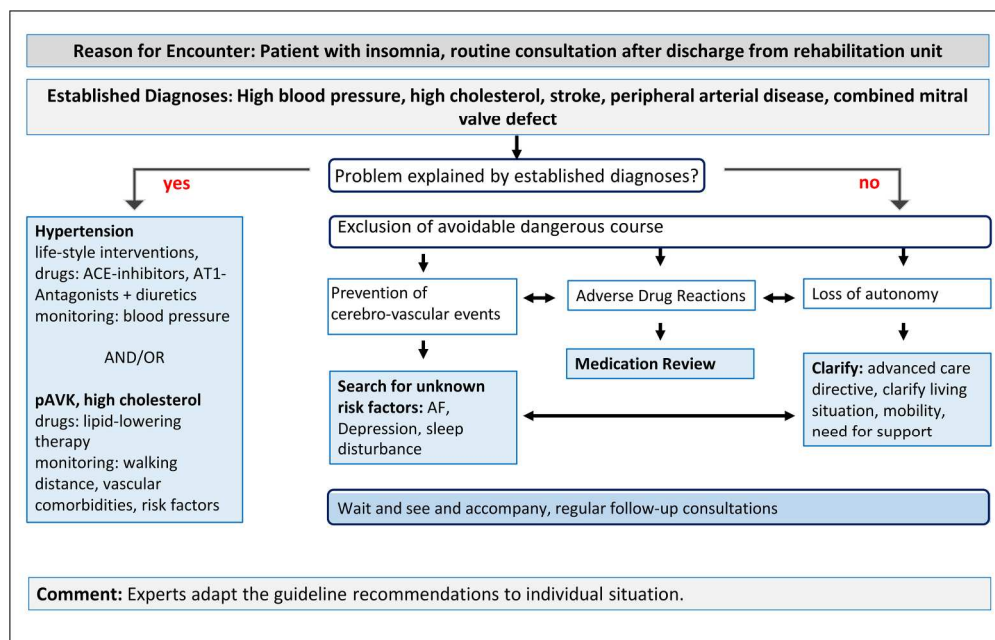
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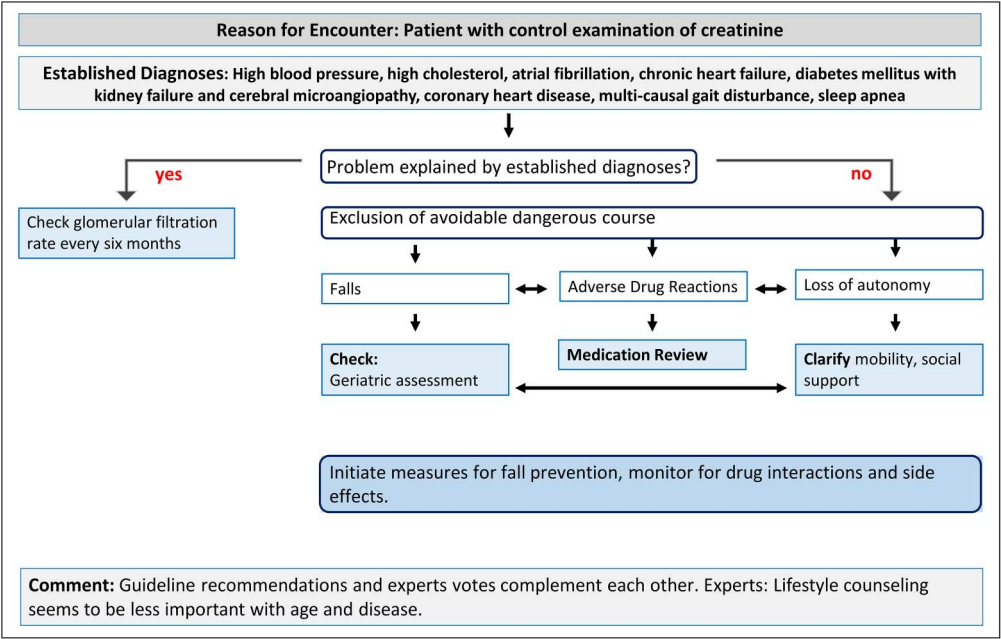


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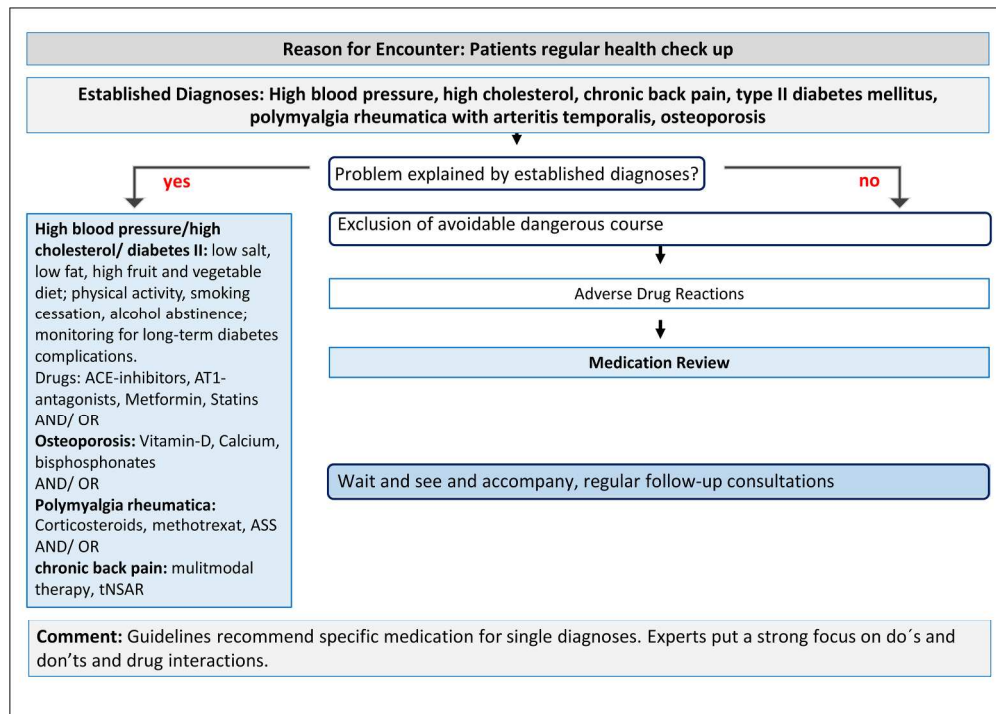


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# BMJ Open

## Development of a meta-algorithm for guiding primary care encounters for patients with multimorbidity using evidence-based and case-based guideline development methodology

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**Development of a meta-algorithm for guiding primary care encounters for patients with multimorbidity using evidence-based and case-based guideline development methodology**

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**ABSTRACT**

**Objective:** the study aimed to develop a comprehensive algorithm (meta-algorithm) for primary care encounters of patients with multimorbidity. We used a novel, case-based *and* evidence-based procedure to overcome methodological difficulties in guideline development for patients with complex care needs.

**Study design:** Systematic guideline development methodology including systematic evidence retrieval (guideline synopses), expert opinions and informal and formal consensus procedures.

**Setting:** Primary care.

**Intervention:** The meta- algorithm was developed in six steps:

1. Designing ten case vignettes of patients with multimorbidity (common, epidemiologically confirmed disease patterns and/or particularly challenging health care needs) in a multidisciplinary workshop.
2. Based on the main diagnoses a systematic guideline synopsis of evidence- and consensus-based clinical practice guidelines was prepared. The recommendations were prioritized according to the clinical and psychosocial characteristics of the case vignettes.
3. Case vignettes along with the respective guideline recommendations were validated and specifically commented on by an external panel of practicing general practitioners (GPs).
4. Guideline recommendations and experts’ opinions were summarized as case specific management recommendations (N-of-one-guidelines).
5. Health care preferences of patients with multimorbidity were elicited from a systematic literature review and supplemented with information from qualitative interviews.
6. All N-of-1-guidelines were analysed using pattern recognition to identify common decision nodes and care elements. These elements were put together to form a generic meta-algorithm.

**Results:** The resulting meta-algorithm reflects the logic of a GP’s encounter of a patient with multimorbidity regarding decision-making situations, communication needs and priorities. It can be filled with the complex problems of individual patients and hereby offer guidance to the practitioner. Contrary to simple, symptom-oriented algorithms the meta-algorithm illustrates a superordinate process which permanently keeps the entire patient in view.

**Conclusion:** The meta-algorithm represents the back bone of the multimorbidity guideline of the German College of General Practitioners and Family Physicians. This article presents solely the development phase, the meta-algorithm needs to be piloted before it can be implemented.

### STRENGTHS AND LIMITATION OF THE STUDY

This is the first study to attempt a case-based "bottom-up" approach to developing a guideline for patients with multimorbidity and complex care needs in primary care.

A methodological approach consisting of quantitative and qualitative methods was used to combine research evidence, experts' opinions and patients' preferences.

The meta-algorithm in its final form was formally consented by the multidisciplinary guideline group that is led by the German College of General Practice and Family Medicine (DEGAM).

For reasons of convenience the number of underlying case vignettes was limited to ten, hereby narrowing the covered spectrum of multimorbidity.

It cannot be excluded that our sample of GPs is a selection of excellence and they might not be representative for the whole sample of all practicing primary care physicians caring for multimorbid patients.

INTRODUCTION

Background

Multimorbidity, defined as the presence of several chronic conditions in one person, is a very common phenomenon in the elderly. It is still difficult to quantify unequivocally how many people suffer from multimorbidity as there is no general consensus on the definition or measurement of multimorbidity. (1) Which conditions contribute to multimorbidity and how many of them need to be present to constitute multimorbidity are particularly controversially debated questions. The lack of a definition explains the large differences in reported prevalence figures which depend on the disease spectrum included, the setting and the data sources used, and the time period assessed. (2–5)

The consequences of multimorbidity for the patients include functional disabilities, a lower quality of life, higher mortality, higher usage of the healthcare system, and thus higher costs. (1, 6–8) The complex care needs of patients with multimorbidity present a particular challenge for the patients themselves and for their care providers. The best explored and most widely discussed care problem is the polypharmacy associated with multimorbidity. This phenomenon is characterized by incalculable interactions of medications and illnesses, adverse effects or contradictory therapeutic strategies. (9, 10) Furthermore, assistive non-pharmaceutical therapies, educational interventions, self-care measures and frequent follow-ups recommended by different individual disease guidelines contribute to the treatment burden of patients with multimorbidity. Patients with 12 different daily medications and 24 daily treatment routines - as demonstrated in the frequently cited case by Boyd 2005 – are often encountered in primary care. (11)

Given the complexity of health problems in patients with multimorbidity, there is wide consensus that the concept of "patient-centered care" should guide any approach to care. (12) The central aspects of the concept include the pursuit of a biopsychosocial disease concept, the pivotal role of patients' central values and priorities, a doctor-patient relationship, shared decision-making and a coordinated approach to interdisciplinary care. (13, 14)

Muth et al. in 2014 formulated a set of principles ("Ariadne principles") specifically for the general practice setting with the intention to guide primary care consultations of patients with multimorbidity. (15) The principles follow the concept of patient-centered care and address the classic responsibilities of primary care: treating current problems, treating chronic problems, clarifying and coordinating patients' and doctors' expectations concerning treatment planning and opportunistic healthcare promotion. (16)

Multimorbidity in Clinical Practice Guidelines

So far, there is only one published clinical practice guideline (CPG) explicitly focussing on the care of patients with multimorbidity. (17) The guideline published by the British National Institute of Excellence



(NICE) takes a wide scope by addressing all health care professionals as well as patients, their families and caregivers. The German primary care guideline "Multimedikation" (Polypharmacy) addresses medication for patients with multimorbidity, but cannot depict the entire primary care process for this particular group of patients. (18) Clinical practice guidelines for single diseases rarely address multimorbidity. (15, 17, 19, 20) Applying the various recommendations of all applicable single disease guidelines is barely feasible and associated with a high risk for the patients due to interactions and incompatible treatments. (11)

Aside from the clinical complexity, guideline development for patients with multimorbidity bears methodological challenges. Five methodological steps are essential for the process of developing evidence-based and consensus-based clinical practice guidelines

- 1) Assembly of a representative, interdisciplinary and multi-professional guideline development group including experts, users and patients.
- 2) Identification of the clinically relevant key questions, which lead to the guidelines' main recommendations.
- 3) Systematic search for the best available empirical evidence to support the recommendations.
- 4) Appraisal of the available evidence from a clinical point of view, with a focus on relevant effects in daily practice and feasibility.
- 5) Structured, reproducible and independently moderated consensus rounds to finalize recommendations. (21, 22)

This classic, data- and expert-based "Top-Down" procedure has not proven particularly helpful in developing a guideline for the treatment of multimorbid patients due to the above-mentioned complexity. Using chronic heart failure and 18 common comorbidities as an example, Muth et al. clearly outlined the various interactions between an index illness and a patient's comorbidities, disease-drug interactions, and drug-drug interactions, (247 interactions, averagely 14 per comorbidity). (23) All of these would need to be considered during the systematic evidence review in the Top-Down guideline development procedure. The implementation of such a procedure for multimorbidity does not seem feasible, especially without focussing on a particular index illness.

#### OBJECTIVE

Against this background, we elaborated and tested a "bottom-up" procedure to develop a comprehensive algorithm to guide a primary care encounter of a patient with multimorbidity. The algorithm aims to give primary care encounters of patients with multimorbidity a structure. It is

intended to support the setting of priorities in patients with complex care needs. The algorithm is intended to be the centerpiece of an evidence- and consensus-based clinical practice guideline "Multimorbidity" (work in progress), created under the supervision of the German College of General Practitioners and Family Physicians (DEGAM). [<http://www.awmf.org/leitlinien/detail/anmeldung/1/II/053-047.html>] The multidisciplinary guideline panel was comprised of GPs, geriatricians, gerontologists, psychologists and health scientists with expertise in evidence-based medicine and guideline development.

**METHODS**

**General approach**

The "bottom-up" procedure for guideline development is based on case vignettes of multimorbid patients. Individual management recommendations were generated for each case vignette, using standard guideline development methodology (problem identification/ formulation of key questions, evidence search and analysis, contextualization, consensus-finding). As in the "N-of-one-trials" (scientific studies with only one participant) (24), the resulting recommendations were considered "N-of-one-guidelines". Using a qualitative synthesis of the N-of-one-guidelines, a generic meta-algorithm was created that reflects management considerations for patients with multimorbidity in primary care. Figure 1 outlines the methodological steps and groups participating in the development process. The process was coordinated and largely realized by the Guideline Working Group which consisted of three general practitioners and three experts in guideline development methodology.

Figure 1

In detail, six methodical steps were followed to develop the meta-algorithm for the management of patients with multimorbidity in primary care:

**Development of Case Vignettes**

Ten Case vignettes of prototypic patients with multimorbidity consulting their GP were constructed in a single day workshop with 20 interdisciplinary (GPs, methodologists, including the Guideline Working Group) participants (Workshop Group). We chose ten vignettes in order to be able to depict the most frequently seen multimorbidity patterns and disease combinations and be able to reflect particularly problematic combinations as seen by the GPs. Disease combinations for two thirds of the vignettes were taken from epidemiological research: typical multimorbidity patterns (cardiovascular/metabolic; anxiety/depression/somatic disorders/pain-oriented morbidity; neuropsychiatric illnesses) reported in the Multicare Study (25) and frequently encountered disease combinations published by van den Bussche et al., 2011 (26). Disease combinations for one third of the vignettes were derived from particularly difficult cases of multimorbidity presented by the participating general practitioners.

Information on the clinical and psychosocial context of each case was collected based on the experience of the task force participants.

Each case vignette contained information on:

- Demographics (Age, Gender, Occupation),
- The patient's medical history,
- Reason for consultation, main complaints/ health problem, and symptoms;
- Diagnoses which constitute the patient's "Multimorbidity",
- Psychosocial context (e.g. marital status, housing situation etc.),
- Results of current examinations (clinical examinations or blood work),
- Medications (name, dosage, application form, prescription data),
- Psychosocial status.

### **Evidence search and analysis**

The evidence base used in creating the management recommendations for each case vignette was derived from published evidence-based and consented clinical practice guidelines. A guideline synopsis was prepared for each case vignette including recommendations from guidelines that address the diagnoses that constitute multimorbidity in the respective vignette. In May 2013 the National Guideline Databases of the Association of Scientific Medical Societies (AWMF) and of the Agency for Quality in Medicine (AQuMed) were searched using the main diagnoses as search terms to create this base of evidence. Guidelines were included if they were up-to-date and contained a systematic work-up of the research evidence (see supplementary file 1). In a first step, all guideline recommendations that applied to the main diagnoses of the case vignettes and that addressed aspects of long-term care of chronic illnesses were extracted by the scientific staff of the guideline working group. Recommendations referring to diagnostic procedures or emergency treatments were not considered. In a second step, the relevant guideline recommendations were identified and prioritized for each case vignette in a modified Delphi procedure by the clinical members of the guideline working group. Recommendations that seemed applicable - taking into consideration demographics, main ailments, psychosocial context, current medication and any additional information to the patient's current life situation - were added to the case vignettes.

**Adding clinical expertise**

All case vignettes and guideline recommendations were clinically validated by practicing general practitioners (GP panel). The GPs were recruited from the server list of an E-Mail-based professional discussion forum led and used by about 700 practicing primary care physicians from all over Germany. The members of the server's list were asked, if they were interested in participating in a research project pertaining to the healthcare of multimorbid patients. All interested physicians received 10 electronic documents containing the case vignettes, a summary of the guideline recommendations and a questionnaire. The questionnaire consisted of three open-ended questions: 1) the necessity to avert life threatening conditions, 2) the definition of management goals and 3) relevant lifestyle and psychosocial factors to be taken into consideration. Additionally, GPs were asked whether they referred to the guideline recommendations contained in the case vignettes when answering the questions. Participants were offered a compensation of 100 €.

**Developing N-of-one-guidelines**

In a next step, the primary care process for each case vignette was displayed as an algorithmic graph (N-of-one-guideline) based on guideline recommendations and clinical judgement. Each N-of-one-guideline starts off with the reason for the patient's current consultation. The key questions guiding the care process are generated from the case vignettes with their heterogeneous multimorbidity constellations and psychosocial contexts. The recommendations referring to the key questions are derived from the external evidence (guideline recommendations) and the GP panel comments. All N-of-one-guidelines were finalized in an informal consensus procedure within the guideline working group.

**Bringing in the patient's perspective**

Taking the values and preferences of the affected patient group into consideration is an essential step in guideline development. (21) Two approaches were taken in order to clarify the preferences and values of patients with multimorbidity regarding their healthcare: 1) a systematic review of qualitative and quantitative studies and 2) qualitative interviews with 15 multimorbid patients sampled from the Multicare cohort study. (27) This process was part of a dissertation project (RM) which will be published separately. The main methodological aspects and results are documented in the supplementary file 2.

For the systematic literature review Medline and Embase were searched via OVID, starting from inception until March 2015. In order to be included into the review, publications had to contain qualitative or quantitative information elicited from patients with multimorbidity regarding their preferences and values in health care. The methodological quality of the qualitative and quantitative studies was checked using the Giacomini and Cook's, 2000 (28) criteria for qualitative research and a modified Checklist of the Scottish Intercollegiate Guideline Network (29) for quantitative research.

Information from the quantitative studies was extracted into Excel-sheets and summarized qualitatively, hereby identifying relevant categories and subcategories. Information from the qualitative materials was sorted into the same categories and integrated into the summaries. If necessary, new categories were defined.

For the qualitative interviews the patients were matched to the case vignettes as closely as possible (for age, gender, and comorbidities). The interview questions were sorted according to the rundown of a practice consultation and the content analysis was based on the categories identified by the literature analysis (doctor-patient relationship, communication, therapeutic goals, subjective needs and framework conditions).

### **Synthesis of the Meta-Algorithm**

The final product, the generic meta-algorithm to guide primary care consultations of patients with multimorbidity was derived from the 10 N-of-one guidelines in an informal, qualitative, synthesis procedure. All N-of-one guidelines were reviewed with the goal of identifying common key questions, decision-making processes, necessary information resources, health care consequences, patient preferences and context considerations ("pattern recognition"). Common elements and interconnections were reformulated, generalized (not related to a particular patient) and combined to create an algorithm that structures a primary care consultation of a patient with multimorbidity. The final version of the meta-algorithm was consented in a nominal group process by the multidisciplinary guideline development group that is led by the German College of General Practitioners and Family Physicians (DEGAM).

## **RESULTS**

### **Case Vignettes of patients with multimorbidity**

Ten case vignettes were established within the one-day workshop by the multidisciplinary working group. Seven vignettes were based on epidemiologically confirmed disease patterns (25, 26) and three vignettes are based on real patients with highly complex multimorbidity reported by the participating GPs (see table 1). In these cases, multimorbidity is constituted not only by clearly defined diseases but also by symptoms such as fatigue or gait disturbance. The patients' ages and psychosocial backgrounds in all vignettes were contributed by the GPs who reflected on situations likely to complicate medical care, self-management and/or communication.

Table 1: Overview of case vignettes

Demography	Psychosocial Context	Diagnoses
Epidemiologically confirmed disease patterns (25)		
91 years male (figure 1)	His wife suffered a stroke, the couple lives secluded	Depression, dementia, coronary heart disease (+ urinary incontinence and hearing loss)
66 years female (supplementary file 3)	Retired, no further information	Chronic back pain, osteoporosis, headaches
82 years female (supplementary file 4)	Immigrated, speaks no German	Chronic heart failure, chronic kidney failure, low blood pressure
55 years female (supplementary file 5)	Immigrated, familial problems, doesn't speak German well	High blood pressure, type II diabetes mellitus, metabolic syndrome
Most frequently encountered disease combinations (26)		
82 years male (supplementary file 6)	Widowed, lives alone, daughter visits every four weeks	High blood pressure, atrial fibrillation, depression
60 years male (supplementary file 7)	Dock worker, shift work, smoker	High blood pressure, coronary artery disease, chronic back pain
84 years female (supplementary file 8)	Lives alone, ambulatory care gives medications	Atrial fibrillation, heart failure, dementia, fatigue
Highly complex real cases, reported by participating GPs		
76 years male (supplementary file 9)	Lives alone, ex-wife cares for him, speech problems	High blood pressure, high cholesterol, stroke, peripheral arterial disease, combined mitral valve defect
80 years male (supplementary file 10)	Retired, no further information	High blood pressure, high cholesterol, atrial fibrillation, chronic heart failure, diabetes mellitus with kidney failure and cerebral microangiopathy, coronary heart disease, multi-causal gait disturbance, sleep apnea
66 years female (supplementary file 11)	Retired, lives alone, no further information	High blood pressure, high cholesterol, chronic back pain, type II diabetes mellitus, polymyalgia rheumatica with arteritis temporalis, osteoporosis

Evidence search and analysis

The guideline search found 27 German (language), up-to-date, evidence- and consensus-based clinical practice guidelines addressing diagnoses and symptoms that constitute multimorbidity in the case vignettes. The number of guidelines to be considered per case vignette varied between two and 22.

Between 59 and 320 (average 138) of the guideline recommendations with potential relevance for a respective case vignette were extracted. These data extractions were distilled into a case specific guideline synopsis not exceeding two pages. The guideline synopses were added to the case vignette.

### **Adding clinical expertise**

18 GPs of the discussion forum were interested in contributing to the project. They received the 10 case vignettes and guideline synopses along with the questionnaires. Completed documents were finally returned from seven participants (three female and four male GPs). The GP panel's answers to the open questions complemented the guideline recommendations by putting an explicit focus on the cases' psychosocial, cultural, and familial backgrounds. Upholding the patients' autonomy was considered a particularly primary goal for managing patients with multimorbidity. The GP panel stated that they considered the recommendations from the guideline synopses when answering the three main questions but rated them as only partially helpful.

### **Developing N-of-one-guidelines**

The case vignettes themselves, the case-based guideline synopses, and the clinical evaluation by primary care physicians formed the basis for the algorithmic display of primary care processes for each case vignette. In total, ten algorithms (see supplementary files 3-11) were created that depict the cognitive and decision-making processes which GPs and patients work through during a consultation. Figure 2 gives one example.

Figure 2: Case-specific algorithm (N-of-one-guideline)

All ten case-specific algorithms served as intermediate steps for the development of the generic "meta-algorithm" (Figure 3).

### **Patient's Perspective**

Nine relevant research projects were identified and analyzed in the literature analysis (six qualitative studies and three quantitative studies). (30–39) Their results were merged with the results of the qualitative interviews as described above.

Patients' preferences, as expressed in the qualitative studies, were grouped into five main categories: doctor-patient-relationship, subjective health care needs, communication, organizational framework of health care and treatment goals. The categories were not independent of each other. The organizational context of health care (such as health insurance, access, availability of providers) forms the basis for all other categories. Communication enables the build-up of a doctor-patient-relationship as well as the expression of needs and the formulation of health-care goals. The results from the quantitative studies as well as the interviews (40) were fitted into these categories.



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Multimorbid patients want to be seen and treated as individuals and want to participate in the decision-making process regarding their healthcare. Patients expect their GPs to display honesty and a certain amount of authority, in combination with supplying sufficient information and demonstrating openness for alternative approaches to care. At the same time, respect for patients' psychosocial backgrounds and involvement of the patients' families and friends were highly valued. Formal aspects that contribute to a good doctor-patient relationship were named: sufficient time for the consultation and the embedding of a practice into a health care network that facilitates access to specialist care as well as to the non-physician therapeutic professions (e.g. physiotherapy). Among the therapeutic goals patients prioritized the ability to lead an autonomous life. From their point of view cognitive functioning and mobility are pivotal for autonomy, followed by other functional outcomes. The importance of continuous care was repeatedly mentioned, including means of quickly reacting to health changes or deterioration. Patients with multimorbidity furthermore expressed their preparedness to actively work on achieving care goals together with their physicians (Mundt R, Dissertation Medical Faculty of Hamburg University, in progress).

Preferences and values expressed by patients were considered modifying components during the process of establishing the meta-algorithm.

**Synthesis of the Meta-Algorithm**

Review of the 10 N-of-one-guidelines identified a number of common elements: Every vignette sets out with a reason for the current encounter. Since GPs typically provide long-term care to their patients and also take on a coordinating role, the reason for the current encounter is viewed against the background of the patient's long-term medical history, the so called "shared medical history". The shared medical history consists of the factual information on established diagnoses and symptoms as well as of the patient's psychosocial and familial status. Furthermore, a longstanding doctor-patient relationship contributes to the development and knowledge of the patient's values, life goals and preferences for medical care.

In all N-of-one-guidelines the key question was, whether the reason for the current encounter could be explained by facts known from the shared medical history. "Yes" results in a comprehensive or problem-oriented disease management with a number of precise but still generic recommendations for action. In case of "No", investigations on whether an avertable dangerous course of disease can and needs to be avoided are required. Three main and generic foci for these investigations were identified from the n-of-one-guidelines: disease-related problems, adverse drug reactions (or interactions) and an impending loss of autonomy. Again, a number of precise but generic recommendations for action were derived from the N-of-one guidelines.



Figure 3 displays the meta-algorithm as a summary of generic considerations derived from 10 case-vignettes of patients with multimorbidity in a GP encounter. In the N-of-one-guidelines the key question could not always be answered with a clear-cut "Yes" or "No". Thus, a meta-algorithm must allow to swap from the Yes-pathway of actions to the No-pathway and *vice versa* (green arrows in Fig. 3).

Figure 3: Meta-algorithm to guide the care of patients with multimorbidity in general practice

## DISCUSSION

We outlined the development of a case-based *and* evidence-based meta-algorithm to guide the management of patients with multimorbidity in general practices.

The algorithm sets out with a multimorbid patient presenting with an arbitrary reason for encounter. From this starting point the cognitive processes that structure the complex consultation situation are displayed. The consideration of patients' preferences, values and life goals stands in the center of the algorithm and prompts shared decision-making, if desired. Priority setting for either disease management or exclusion of an avoidable dangerous course is determined by the answer to one single key question. Both possible pathways are completed by generic recommendations of medical and social aspects to be covered, possible diagnostic, therapeutic and management steps to be taken and information resources to be used. The whole process is embedded in the typical GP setting with a longstanding patient-doctor relationship as the basis for a "shared medical history". On the whole, the meta-algorithm encompasses the main criteria for patient-centered care. (14, 41, 42) The meta-algorithm was distilled from ten evidence- and consensus-based N-of-one-guidelines dealing with the GP management of ten patients with heterogeneous multimorbidity (case-vignettes). The ten case vignettes were constructed to represent the most frequently encountered disease combinations as well as particularly challenging complex situations presented by practicing GPs. The N-of-one-guidelines were developed by the guideline working group, a panel of GPs and methodologists.

As a whole, the meta-algorithm reflects the logic of a GP encounter of a patient with multimorbidity regarding explicit aspects to consider, decision situations, and communication needs and priorities. It can be filled with the complex problems of individual patients and hereby offer guidance to the individual practitioner. Contrary to simple, symptom-oriented algorithms, the "meta-algorithm" illustrates a superordinate process which permanently considers all aspects of a patient. The decision-making processes are primarily guided by the reason for encounter, not by specific diagnoses or combinations of diagnoses. Naturally, avoiding an avertable, dangerous course of disease is a main priority in GP-care – provided it is compatible with the individual patient's values and preferences. Especially avoiding the loss of autonomy and maintaining independence (in the sense of the patients' abilities to lead their own lives) has gained new priority as could be gathered from the N-of-one-

guidelines and the information regarding patients' preferences. This goal may - in individual cases - even supersede solely disease-oriented guideline-based management decisions. Still, disease specific, evidence- and guideline-based recommendations play a pivotal role in disease management, if embedded in the holistic care process.

The meta-algorithm in its final form was consented by the multidisciplinary guideline group that is led by the German Society of General Practice and Family Medicine (DEGAM).

**Strengths and weaknesses of the methodological approach**

To our knowledge this is the first study attempting a bottom-up approach based on case-vignettes of real patients to develop a comprehensive algorithm for managing of patients with multimorbidity. We are aware that ten patients cannot be representative for all multimorbid patients in German general practices. For practical reasons, we restricted our work to 10 patient vignettes which can at least be considered typical patients/situations. Seven out of ten case vignettes obtained common disease combinations from two German epidemiological studies. (25, 26) Three further case vignettes representing particularly challenging patients were developed from real cases presented by the participating GPs in the workshop. As another strength we regard the development of the N-of-one guidelines, because it followed a standard guideline development methodology for evidence- and consensus based clinical practice guidelines.

To make sure that the recommendations in the N-of-one-guidelines are evidence-based a comprehensive search for German evidence- and consensus-based guidelines was performed. Further quality assessment was waived since all retrieved guidelines were of accredited a high-quality (S3-Standard, according AWMF). (43) The prioritisation of recommendations within the development of the N-of-one guidelines was reached by consensus within the guideline working group.

An external GP panel was recruited via an email discussion forum to clinically validate the cases. This small sample of seven GPs is likely a positive selection since participants in this forum have an above-average interest in improving primary care. This disadvantage has to be accounted for in the pilot study, which needs to include a larger and more representative sample of GPs in Germany.

A literature review as well as qualitative interviews were conducted in order to assess the patients' preferences and values regarding the care received through their GPs. The literature search for the review was purposefully kept very specific by using "multimorbidity" as the main search term because we intended to include research that perceives "multimorbidity" as a unique entity instead of comorbidities accompanying a specific index disease. The fact, that the results from the qualitative

interviews of patients with multimorbidity corresponded well with the results from the literature analysis made us confident that we actually captured the main aspects of the patient perspective.

The meta-algorithm is going to form the centerpiece of the multimorbidity guideline of the DEGAM and has been consented in a formal consensus process for this purpose. The algorithm will be embedded in concrete evidence- and/or consensus-based recommendations concerning communication, management and coordination of care and infrastructural context in the guideline document. The meta-algorithm could, in itself, be useful in structuring primary care encounters outside Germany since it does not refer to a specific infrastructural context.

### Comparison with the literature

Among clinicians but also in the research community there is a consensus that patients with multimorbidity and their multifold healthcare needs pose a major challenge to primary care physicians who are often overwhelmed by the complexity of problems. (44–46) Furthermore, it is agreed, that following the recommendations of every applicable clinical practice guideline for single disorders is neither feasible nor reasonable, taking into account the resulting treatment burden and numerous possible adverse interaction effects. (11, 47, 48) Still, the evidence on the effectiveness of interventions to improve the outcomes of patients with multimorbidity is rather limited. A recent Cochrane Review (49) reported the effectiveness of organizational (twelve RCTs) and patient-oriented (six RCTs) interventions to improve the outcomes of patients with multimorbidity in primary care and community settings. The authors conclude that there is a good amount of uncertainty remaining as concerns the effectiveness of interventions due to the relatively small number of studies available to date and their mixed results. An improvement of the evidence base is to be expected though since the authors identified 15 ongoing trials. Interventions like the meta-algorithm, which would be classified as a professional intervention (50) were not addressed in the review. Still, one of the conclusions the authors of the Cochrane Review came to was that, in order to achieve sustainability, interventions have to integrate with the existing health care system. A requirement that is met by this meta-algorithm.

So far there is still only one clinical practice guideline dealing explicitly with the management of patients with multimorbidity: the guideline "Multimorbidity: clinical assessment and management" issued by the British National Institute for Health and Care (NICE). (17) The guideline was developed via the standard "top-down" approach to guideline development and is based on extensive literature analyses. The NICE guideline addresses not only primary care providers but all health care professionals, including both generalists and specialists. Our meta-algorithm and the NICE guideline do not contradict but complement each other: The meta-algorithm guides clinical reasoning for every GP encounter from a holistic perspective. Medical and psychosocial information from the shared medical history as well as

patients’ preferences, values and life goals communicated in a longstanding doctor – patient relationship back-up and guide priority setting in every new encounter. The meta-algorithm offers guidance to GPs in steering through complex clinical situations and identifying high priority problems while, at the same time, not losing sight of their complexity. The NICE guideline offers a large number of detailed recommendations while lacking the clinical reasoning structure in primary care. The latter may be due to the fact, that the NICE guideline is not confined to primary care but addresses all participants in health care as well as patients, their relatives and caregivers.

Muth et al. present the "Ariadne principles" resulting from an expert workshop and two extensive discussion and feedback rounds among GPs and other experts for multimorbidity in primary care from six countries in North America, Europe and Australia. The principles reflect the core elements of an ongoing counseling process for patients with multimorbidity. (15) The elements of the ariadne principles are also found in our meta-algorithm – clarifying interactions may be part of accompanying disease management or part of investigating the avoidability of a dangerous disease course; respecting patient preferences and the mutual agreement on treatment goals are basic principles for any doctor – patient interaction at the various decision points of the algorithm. The main difference between the two concepts is that the meta-algorithm structures one specific consultation. The reason for the encounter determines priorities for the current consultation, while other aspects are posteriorised and maybe postponed to the next encounter. In this way, the meta-algorithm helps to keep a holistic view on the care of patients with multimorbidity and at the same time prevents overloading the current consultation session.

Another intervention, which has some similarities to the proposed meta-algorithm, has been pilot-tested in an exploratory cluster randomized trial (CARE Plus study). The intervention, which is termed a “whole-system-intervention” was applied in primary care practices in Glasgow and addressed patients with multimorbidity from deprived areas. It consists of longer and structured primary care consultations, the establishment of a care plan and self-help support (CARE Approach). The exploratory trial demonstrated positive effects on some endpoints (negative well-being, quality of life) and indicated that the intervention was cost-effective. (51, 52)

Yet another approach is currently being tested in a pragmatic randomized controlled trial. The 3D study is testing the effectiveness of a novel approach to GP-management of patients with multimorbidity compared to usual care. The intervention is based on a conceptual framework incorporating the patient-centered care model and aims at improving patients’ quality of life, reducing the burden of illness and treatment and improving patients’ care experiences. GPs received specific training and incentives to foster the implementation of the intervention. The trial is scheduled to end in May 2017 [<http://www.isrctn.com/ISRCTN06180958>]. The intervention of the 3D study has some overlaps with the

meta-algorithm, especially in the emphasis on the continuity of care, the co-ordinated holistic review (instead of disease-focused review) and the focus on patients' priorities and needs, quality of life and function and disease management. 3D furthermore focusses on detecting depression which is not explicitly addressed in the meta-algorithm. (53)

To prepare the implementation of the meta-algorithm it will be embedded into the clinical practice guideline "Multimorbidity" of the German College of General Practitioners and Family Physicians. The guideline itself will be pilot tested in a sample of GP practices in northern Germany with a primary focus on feasibility and practicability. After necessary modifications are made based on the evaluation results, a quantitative evaluation is planned to investigate the process and patient outcomes. Therefore, the implementation of the meta-algorithm will ideally be complemented by the use of a classification system such as the ICPC. This system can be used to document multiple episodes of care in one patient over time. (54)

## Conclusion

The case-based and evidence-based meta-algorithm presented here provides guidance on handling multimorbidity in primary care. It incorporates the principles of patient-centered care. The bottom-up development based on n-of-one-guidelines was based on research evidence as well as on GPs' clinical expertise. In turn, applying the meta-algorithm will enable in individualized evidence-based care. The next steps will incorporate the implementation and testing of the meta-algorithm in practices as a part of a clinical practice guideline.

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**Footnotes**

Cathleen Muche-Borowski (CMB) AND Dagmar Lühmann (DL) contributed equally.

**Contributors:** Martin Scherer (MS) was responsible for conceptual design of the case-based guideline development. IS contributed the epidemiological basis for the case vignettes. All authors contributed to the development of the case vignettes. Hans-Otto Wagner (HOW) and MS contributed clinical expertise. CMB and DL were responsible for the guideline synopsis. HOW, CMB and DL synthesized the N-of-1-guidelines. Rebekka Mundt (RM) performed literature analysis and interviews for patient preferences. All authors contributed to the compilation of the meta-algorithms. CMB and DL drafted manuscript. The final version of the paper has been reviewed and approved by all authors, including the DEGAM guideline group.

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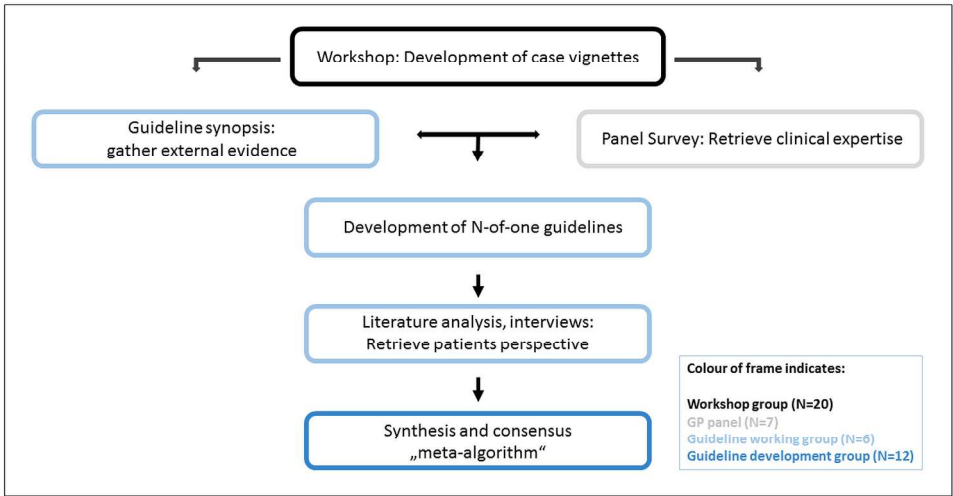
54. Laux G, Kuehle T, Rosemann T, Szecsenyi J. Co- and multimorbidity patterns in primary care based on episodes of care: results from the German CONTENT project. *BMC Health Serv Res.* 2008 Jan 18;8:14. doi: 10.1186/1472-6963-8-14.

## FIGURES (LEGENDS)

Figure 1: Methodological steps to develop a "Meta-Algorithm" for the management of patients with multimorbidity

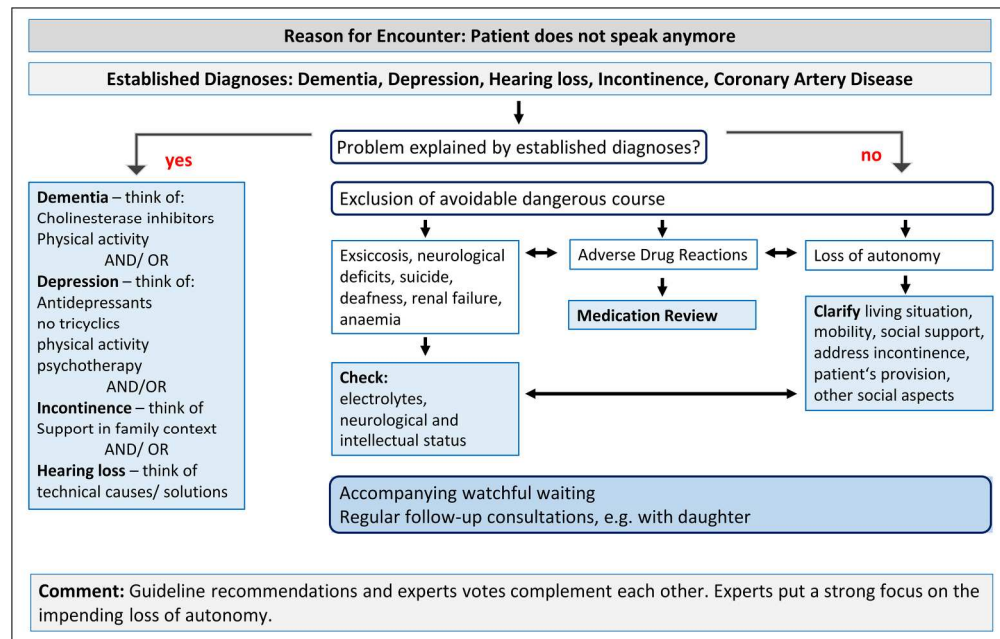
Figure 2: Case-specific algorithm (N-of-one-guideline): The 91-year old patient with multimorbidity presents to his family physician accompanied by his daughter. The reason for encounter is: the patient doesn't speak anymore. Against the background of established diagnosis the GP has to decide whether the new symptom is explained by the known diagnoses. If so, progress will be made towards improved disease management. If not, exclusion of an avoidable dangerous course will be prioritized.

Figure 3: "Meta-Algorithm" to guide care for patients with multimorbidity in general practice



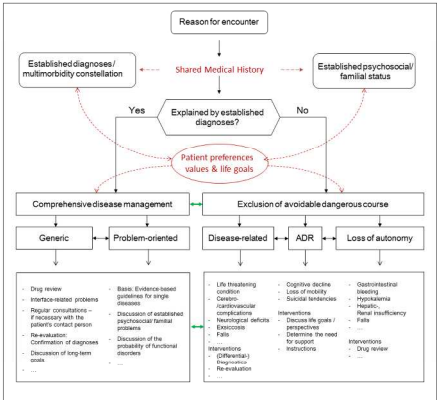
Methodological steps to develop a "Meta-Algorithm" for the management of patients with multimorbidity

338x190mm (300 x 300 DPI)



Case-specific algorithm (N-of-one-guideline): The 91-year old patient with multimorbidity presents to his family physician accompanied by his daughter. The reason for encounter is: the patient doesn't speak anymore. Against the background of established diagnosis the GP has to decide whether the new symptom is explained by the known diagnoses. If so, progress will be made towards improved disease management. If not, exclusion of an avoidable dangerous course will be prioritized.

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„Meta-Algorithm“ to guide care for patients with multimorbidity in general practice

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## Web appendix 1: Overview of included guidelines

Diagnosis	Guideline
<b>Hypertension</b>	Neue Entwicklungen in der Hochdrucktherapie 2011; Deutsche Hochdruckliga e.V. DHL und Deutsche Gesellschaft für Hypertonie und Prävention <a href="https://www.hochdruckliga.de/nachrichtendetails/items/neue-entwicklungen-in-der-hochdrucktherapie.html">https://www.hochdruckliga.de/nachrichtendetails/items/neue-entwicklungen-in-der-hochdrucktherapie.html</a>
	Leitlinien zur Behandlung der arteriellen Hypertonie 2008; Deutsche Hochdruckliga e.V. DHL - Deutsche Hypertonie Gesellschaft <a href="https://www.hochdruckliga.de/bluthochdruck-behandlung-leitlinien.html">https://www.hochdruckliga.de/bluthochdruck-behandlung-leitlinien.html</a>
<b>Atrial fibrillation</b>	Leitlinien für das Management von Vorhofflimmern 2012; Deutsche Gesellschaft für Kardiologie <a href="https://leitlinien.dgk.org/2013/pocket-leitlinien-fur-das-management-von-vorhofflimmern-fokus-update-2012/">https://leitlinien.dgk.org/2013/pocket-leitlinien-fur-das-management-von-vorhofflimmern-fokus-update-2012/</a>
	DEGAM-Leitlinie Nr. 8: Schlaganfall (Kapitel 5.2.2.2 Vorhofflimmern) 2012; Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin <a href="http://www.degam.de/degam-leitlinien-379.html">http://www.degam.de/degam-leitlinien-379.html</a>
<b>Coronary heart disease</b>	Chronische KHK 2006; Nationale VersorgungsLeitlinie <a href="http://www.awmf.org/leitlinien/detail/II/nvl-004.html">http://www.awmf.org/leitlinien/detail/II/nvl-004.html</a>
	Chronische KHK - Modul Medikamentöse Therapie 2011; Nationale VersorgungsLeitlinie <a href="http://www.awmf.org/leitlinien/detail/II/nvl-004.html">http://www.awmf.org/leitlinien/detail/II/nvl-004.html</a>
<b>Chronic heart failure</b>	Chronische Herzinsuffizienz 2012; Nationale VersorgungsLeitlinien <a href="http://www.awmf.org/leitlinien/detail/II/nvl-006.html">http://www.awmf.org/leitlinien/detail/II/nvl-006.html</a>
<b>Heart valve defect</b>	Pocket-Leitlinien: Klappenvitien im Erwachsenenalter 2007; Deutschen Gesellschaft für Kardiologie <a href="https://leitlinien.dgk.org/2007/pocket-leitlinie-klappenvitien-im-erwachsenenalter/">https://leitlinien.dgk.org/2007/pocket-leitlinie-klappenvitien-im-erwachsenenalter/</a>
	Deutsche Leitlinie zur Rehabilitation von Patienten mit Herz-Kreislaufkrankungen 2007; Deutsche Gesellschaft für Prävention und Rehabilitation von Herz-Kreislaufkrankungen e.V. <a href="http://www.dgpr.de/leitlinien-empfehlungen-positionspapiere.html">http://www.dgpr.de/leitlinien-empfehlungen-positionspapiere.html</a>
<b>Dyslipidemia</b>	Hausärztliche Leitlinie - Kardiovaskuläre Prävention 2011; Leitliniengruppe Hessen <a href="http://www.pmvforschungsguppe.de/content/03_publicationen/03_d_leitlinien.html">http://www.pmvforschungsguppe.de/content/03_publicationen/03_d_leitlinien.html</a>
<b>Type II diabetes mellitus</b>	Empfehlungen zur antihyperglykämischen Therapie des Diabetes mellitus Typ 2 2009; Arzneimittelkommission der Deutschen Ärzteschaft <a href="http://www.akdae.de/Arzneimitteltherapie/TE/A-Z/index.html">http://www.akdae.de/Arzneimitteltherapie/TE/A-Z/index.html</a>
	Nierenerkrankungen bei Diabetes im Erwachsenenalter 2010, Nationale VersorgungsLeitlinien <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html</a>
	Neuropathie bei Diabetes im Erwachsenenalter 2011; Nationale VersorgungsLeitlinien <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html</a>
	Präventions- und Behandlungsstrategien für Fußkomplikationen 2006; Nationale VersorgungsLeitlinien (aktuell in der Überarbeitung) <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html</a>
	Prävention und Therapie von Netzhautkomplikationen 2006; Nationale VersorgungsLeitlinien (aktuell in der Überarbeitung) <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html</a>
	Körperliche Aktivität und Diabetes mellitus 2008; Deutschen Diabetes-Gesellschaft

	<a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte- leitlinien.html</a>
	Evidenz-basierte Ernährungsempfehlungen zur Behandlung und Prävention des Diabetes mellitus 2005; Deutsches Diabetes-Zentrum <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-&lt;br/&gt;leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte- leitlinien.html</a>
	Diabetes – Strukturierte Schulungsprogramme 2013; Nationale VersorgungsLeitlinien <a href="http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte-&lt;br/&gt;leitlinien.html">http://www.deutsche-diabetes-gesellschaft.de/leitlinien/evidenzbasierte- leitlinien.html</a>
<b>Dementia</b>	S3-Leitlinie Demenzen 2009; Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde und Deutsche Gesellschaft für Neurologie <a href="http://www.kompetenznetz-demenzen.de/fachpublikum/leitlinien/">http://www.kompetenznetz-demenzen.de/fachpublikum/leitlinien/</a>
	DEGAM-Leitlinie Nr. 12: Demenz 2008; Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin <a href="http://www.degam.de/degam-leitlinien-379.html">http://www.degam.de/degam-leitlinien-379.html</a>
<b>Depression</b>	S3-Leitlinie Unipolare Depression 2013; Nationale VersorgungsLeitlinie <a href="http://www.awmf.org/leitlinien/detail/II/nvl-005.html">http://www.awmf.org/leitlinien/detail/II/nvl-005.html</a>
<b>Back pain</b>	Kreuzschmerz 2011; Nationale VersorgungsLeitlinie <a href="http://www.awmf.org/leitlinien/detail/II/nvl-007.html">http://www.awmf.org/leitlinien/detail/II/nvl-007.html</a>
<b>Osteoporosis</b>	Prophylaxe, Diagnostik und Therapie der Osteoporose bei Erwachsenen 2009; Dachverbandes Osteologie (DVO) <a href="http://www.osteoporose-portal.de/arzt/DVO-LL-2010">http://www.osteoporose-portal.de/arzt/DVO-LL-2010</a>
<b>Headache</b>	Umgang mit Patienten mit nicht-spezifischen, funktionellen und somatoformen Körperbeschwerden 2012; Deutsche Gesellschaft für Psychosomatische Medizin und Ärztliche Psychotherapie e.V. und Deutsches Kollegium für Psychosomatische Medizin <a href="http://www.awmf.org/leitlinien/detail/II/051-001.html">http://www.awmf.org/leitlinien/detail/II/051-001.html</a>
<b>Polymyalgia rheumatica</b>	Ness T, Bley TA, Schmidt WA, Lamprecht P: Diagnose und Therapie der Riesenzellarteriitis. Dtsch Arztebl Int 2013; 110(21): 376–86. <a href="https://www.aerzteblatt.de/archiv/138880/Diagnose-und-Therapie-der-Riesenzellarteriitis">https://www.aerzteblatt.de/archiv/138880/Diagnose-und-Therapie-der-Riesenzellarteriitis</a>
<b>Sleep apnea</b>	Therapie der obstruktiven Schlafapnoe des Erwachsenen 2009; Dt. Ges. f. Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie <a href="https://www.hno.org/publikationen/leitlinien.html">https://www.hno.org/publikationen/leitlinien.html</a>
	S3-Leitlinie – Nicht erholsamer Schlaf/Schlafstörungen 2009; Deutsche Gesellschaft für Schlafforschung und Schlafmedizin <a href="http://www.dgsm.de/">http://www.dgsm.de/</a>



## Web appendix 2: Methodology of literature analysis on patient preferences

### Literature Search

We used a combined search strategy for qualitative and quantitative studies investigating health care preferences of patients with multimorbidity. The search strategy consisted of three modules (multimorbidity, patient preferences and study design). Within the modules the search terms were combined using the operator "OR", the three modules were combined using the operator "AND".

Table 1 App 2: Search terms and modules

multimorbidity	patient preferences	study design
multimorbid*	„patient* centered“	„focus group“
comorbid*	„patient* satisfaction“	interview
„frail elderly“	„patient* view“	survey
	„patient* perception“	„mixed method*“
	„patient* perspective“	„qualitative study“
	„patient* preference“	„qualitative research“
	expectation*	

Search strategy for Medline and Embase via Ovid (inception to March 2015):

((((((("qualitative study") OR "Qualitative Research"[Mesh]) OR "mixed method\*") OR survey) OR interview) OR "Focus Groups"[Mesh])) AND (((("Comorbidity"[Mesh]) OR multimorbid\*) OR "Frail Elderly"[Mesh])) AND (((((((("Patient Preference"[Mesh]) OR "patient\* perspective") OR "patient\* perception") OR "patient\* view") OR "patient\* satisfaction") OR "patient\* centered") OR expectation\*). The search yielded 650 hits after removal of duplicates.

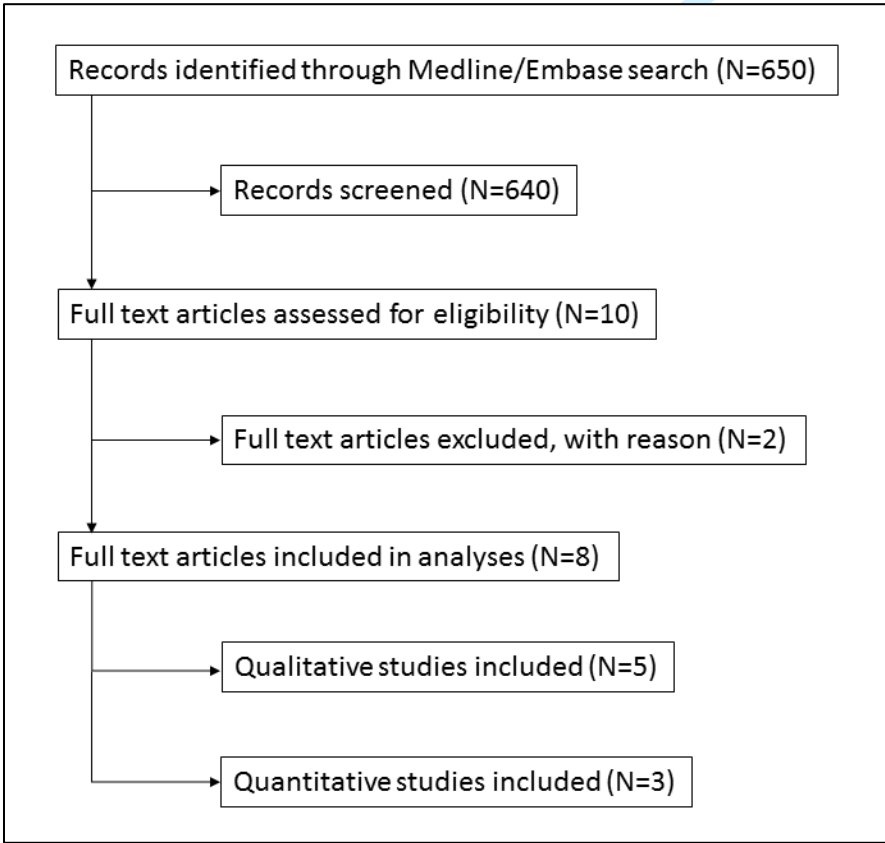
Inclusion/exclusion criteria

Table 2 App 2: In- and exclusion criteria in the literature analysis

	Inclusion criteria	Exclusion criteria
patients	patients with multimorbidity ≥ 2 diseases	studies reporting on patients with a specific index disease and comorbidities;
study objective	investigation of patients’ healthcare preferences and priorities	effectiveness studies to improve the outcomes of patients with multimorbidity
Study design - qualitative studies	any qualitative study with a transparently documented state-of- the-art methodological approach; systematic reviews of qualitative studies with a transparently documented methodological approach	studies without transparently documented state-of-the-art methodological approach; unsystematic reviews
Study design – quantitative studies	cross-sectional studies, surveys, baseline examination of prospective studies	

After removal of duplicates 650 hits remained to screened for inclusion into the review.

Figure 1 App 2: Flow Chart of literature selection



## Characteristics of included studies

Table 3 App 2: Study characteristics of included studies – Qualitative studies

1 <sup>st</sup> author, year, country	Objective	Inclusion criteria	Exclusion criteria	Participants	Methodology	Quality criteria*
Robben et al., 2011 Netherlands	Investigation of preferences for receiving information among frail elderly (and their informal care givers).	'frail elderly' over 65, defined as: more than 1 of: cognitive impairment; physical handicap; psychosocial problems; multimorbidity; polypharmacy; social isolation. (Dutch College of General Practitioners)	unable to speak (Dutch); severe hearing loss; life expectancy < 6 months; severe cognitive deficits.	f: 9 m: 2	semi-structured interviews; grounded theory	10/11
van Kempen et al., 2011 Netherlands  <i>same study as Robben et al. 2011</i>	Investigation of the needs and preferences of frail older people concerning home visits of family physicians.	'frail elderly' over 65, defined as: more than 1 of: cognitive impairment; physical handicap; psychosocial problems; multimorbidity; polypharmacy; social isolation. (Dutch College of General Practitioners)	unable to speak (Dutch); severe hearing loss; life expectancy < 6 months; severe cognitive deficits.	f: 9 m: 2	semi-structured interviews; grounded theory	10/11

1 <sup>st</sup> author, year, country	Objective	Inclusion criteria	Exclusion criteria	Participants	Methodology	Quality criteria*
Ekdahl et al., 2010 Sweden	Investigation of patients' preferences for shared decision making when admitted to hospital for an acute illness.	'frail elderly' as defined by the Swedish National Centre of Epidemiology 2001: > 75 years, > 3 hospital stays within the last 12 months, > 3 ICD-10 diagnoses	unable to speak (Swedish), substantial dementia	f: 10 m: 5	semi-structured interviews; content analysis according to Graneheim and Lundman with manifest and latent focus.	11/11
Fried et al., 2008 USA	Investigating multimorbid patients views on and knowledge about drug effects and interactions.	≥ 65 years ≥ 5 drugs 16 further criteria characterizing multimorbidity.	unable to speak (English); severe hearing loss; severe cognitive deficits.	f: 44 m: 22	13 focus groups; grounded theory	10/11
Bayliss et al., 2008 USA	Explore processes of care desired by elderly patients who have multimorbidities.	≥ 65 years at least: diabetes, depression, osteoarthritis; stratified random sample from survey respondent population; members of one HMO	n.g.	f: 13 m: 13	face-to-face, semi-structured interviews, content analysis	9/11
Noel et al., 2005 USA	To explore the collaborative care needs and preferences in primary care patients with multiple chronic illnesses.	Veterans Health Administration, primary care clinics (found by purposive sampling): ≥ diagnoses	severe cognitive impairment; uncontrolled psychiatric illness	f: 12 m: 48	focus groups, content analysis	8/11

1 <sup>st</sup> author, year, country	Objective	Inclusion criteria	Exclusion criteria	Participants	Methodology	Quality criteria*
Jerant et al., 2005	(1) to elicit perceived barriers to active self-management; and (2) to elicit perceived barriers to accessing self-management support services and resources.	convenience sample from university: (1) diagnosis of one or more of the study chronic illnesses (arthritis, asthma, COPD, CHF, depression, and DM); (2) aged 40 or older; (3) able to read at 7th grade level and speak English; (4) residing in a private home; and (5) interest in discussing chronic illness self-management. (85% had ≥ 2 chronic illnesses)	n.g.	f: 37 m:17	focus groups content analysis	10/11
f: female; m: male; n.g.: not given *criteria derived from Giacomini and Cook 2000						

Table 4 App 2: Study characteristics of included studies – quantitative studies

1 <sup>st</sup> author, year, country	Objective	Inclusion criteria	Exclusion criteria	Participants	Methodology	Quality criteria*
<b>Quantitative studies</b>						
Killiari et al., 2014 Cyprus	Investigation of prevalence of multimorbidity in Cyprus and patients' satisfaction with health care.	Patients with ≥ 2 diagnoses, 18-88 years, representative household sample, excluding institutional residents and group housings.	n.g.	f: 264 m: 201	cross-sectional study, personal interviews	3/6
Fung et al., 2008 USA	Investigate relationship between multimorbidity and patient's rating of communication.	Random sample of households from 12 communities with > 200.000 inhabitants drawn from the CTS Household Surveys national sample.	n.g.	f: 8204 m: 7505	cross-sectional study, telephone interviews	4/6
Noel et al., 2007 USA	Comparison of need for self-management-education between patients with multimorbidity and patients with single diseases.	Patients from a 'Veterans Affairs Medical Center' with at least 1 contact over the last 13 months. Either multimorbid patients (≥ 3 diagnoses) or patients with just one chronic disease	n.g.	patients with multimorbidity: n = 227 patients with single disease: n=195	cross-sectional study	5/6
f: female; m: male; n.g.: not given *criteria: participant selection; responder/ non-responder; clearly focused endpoint definition; validated questionnaires; measurement if confounding variables; documentation of missing values						

## Excluded studies with reasons

Table 5 App 2: Excluded studies

Study	Reason for exclusion
Junius-Walker et al.: Impact of a priority-setting consultation on doctor-patient agreement after a geriatric assessment: cluster randomised controlled trial in German general practices. Qual Prim Care. 2012;20(5):321-34.	Interventional study
Wrede J et al.: Complex health care decisions with older patients in general practice: patient-centeredness and prioritization in consultations following a geriatric assessment. Patient Educ Couns. 2013 Jan;90(1):54-60  <i>same study as Junius-Walker et al.</i>	Interventional study
Löffler C et al.: Optimizing polypharmacy among elderly hospital patients with chronic diseases--study protocol of the cluster randomized controlled POLITE-RCT trial. Implement Sci. 2014 Oct 6;9:151.	Study protocol

References

Ekdahl AW, Andersson L, Friedrichsen M. "They do what they think is the best for me." Frail elderly patients' preferences for participation in their care during hospitalization. *Patient Educ Couns*. 2010;80(2):233–40.

Robben S, van Kempen J, Heinen M, Zuidema S, Olde Rikkert M, Schers H, u. a. Preferences for receiving information among frail older adults and their informal caregivers: a qualitative study. *Fam Pract*. 2012;29(6):742–7.

van Kempen JAL, Robben SHM, Zuidema SU, Olde Rikkert MGM, Melis RJF, Schers HJ. Home visits for frail older people: a qualitative study on the needs and preferences of frail older people and their informal caregivers. *Br J Gen Pract J R Coll Gen Pract*. 2012;62(601):e554-60.

Fried TR, McGraw S, Agostini JV, Tinetti ME. Views of older persons with multiple morbidities on competing outcomes and clinical decision-making. *J Am Geriatr Soc*. 2008;56(10):1839–44.

Noël PH, Frueh BC, Larme AC, Pugh JA. Collaborative care needs and preferences of primary care patients with multimorbidity. *Health Expect Int J Public Particip Health Care Health Policy*. 2005;8(1):54–63.

Bayliss EA, Edwards AE, Steiner JF, Main DS. Processes of care desired by elderly patients with multimorbidities. *Fam Pract*. 2008;25(4):287–93.

Jerant AF, von Friederichs-Fitzwater MM, Moore M. Patients' perceived barriers to active self-management of chronic conditions. *Patient Educ Couns*. 2005;57(3):300–7.

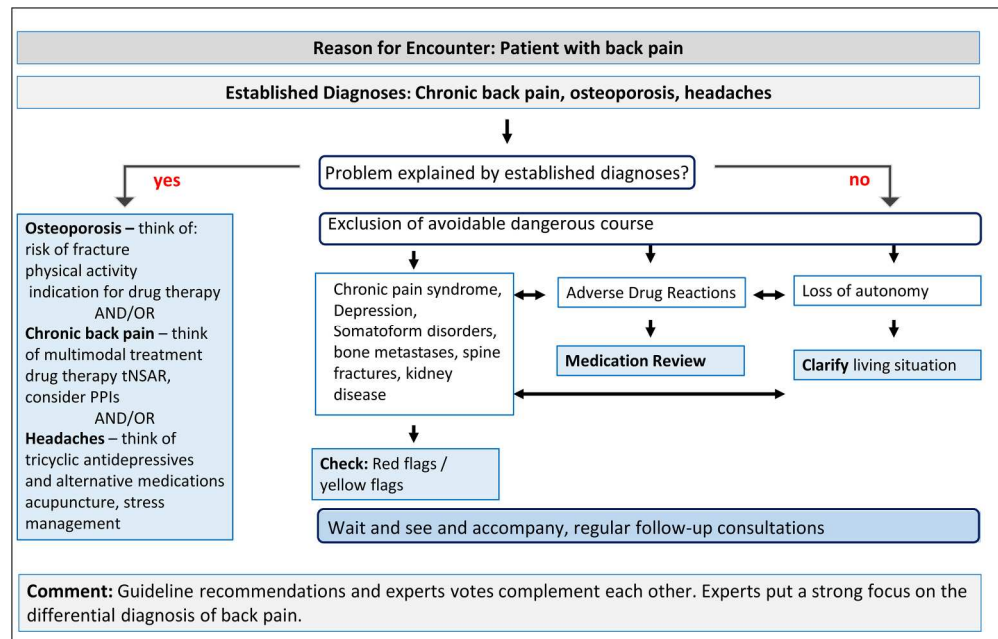
Kiliari N, Theodosopoulou E, Papanastasiou E. Multimorbidity and unmet citizens' needs and expectations urge for reforms in the health system of Cyprus: a questionnaire survey. *JRSM Open*. 2014;5(1):2042533313515860.

Fung CH, Setodji CM, Kung F-Y, Keesey J, Asch SM, Adams J, u. a. The relationship between multimorbidity and patients' ratings of communication. *J Gen Intern Med*. 2008;23(6):788–93.

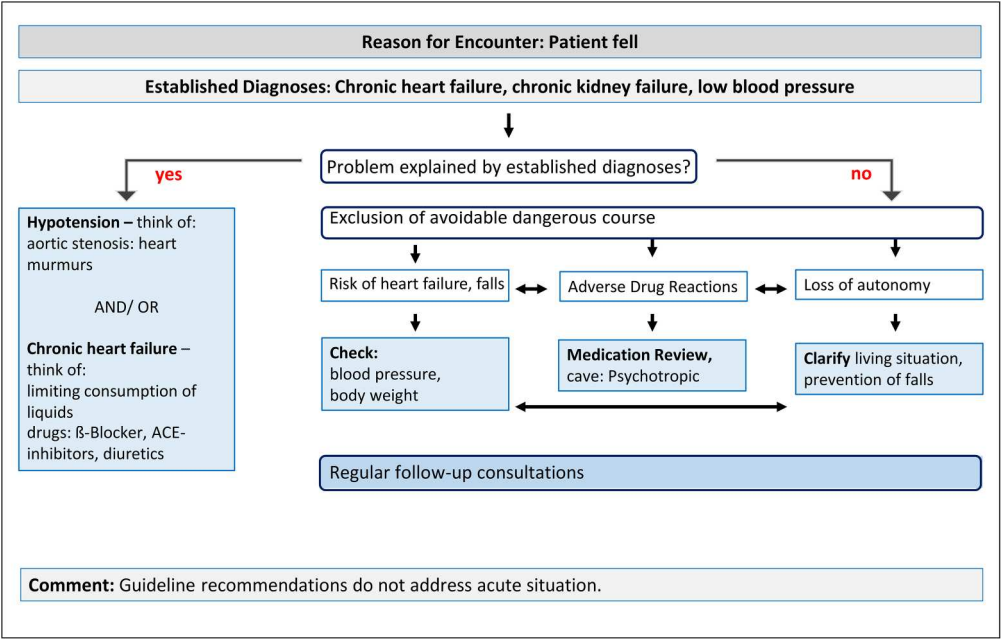
Noel PH, Parchman ML, Williams JWJ, Cornell JE, Shuko L, Zeber JE, u. a. The challenges of multimorbidity from the patient perspective. *J Gen Intern Med*. 2007;22 Suppl 3:419–24.

Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA*. 19. Juli 2000;284(3):357–62.

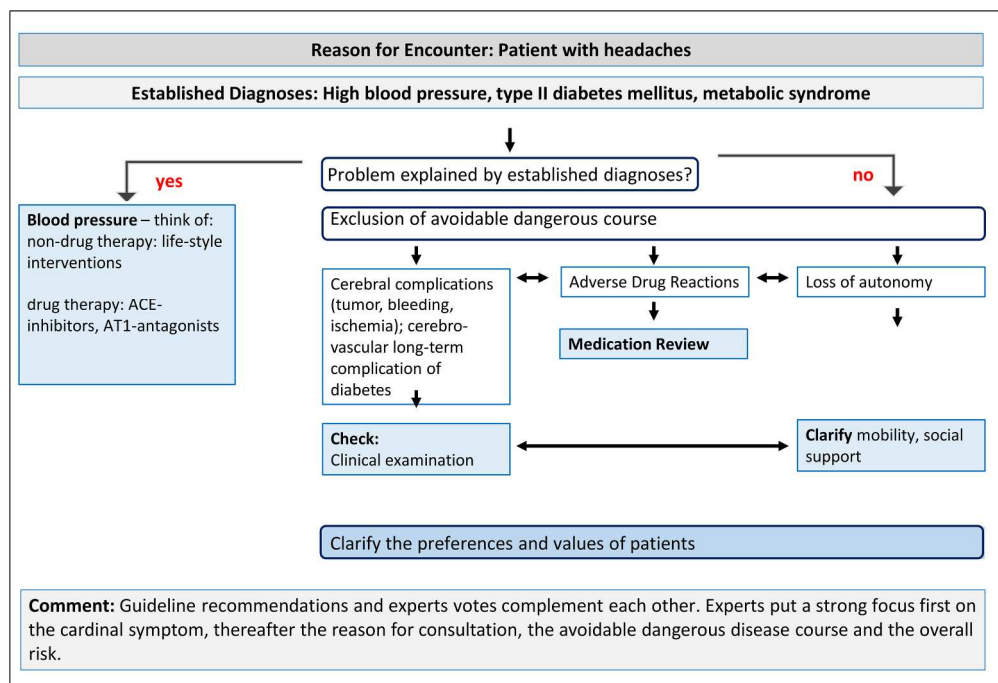




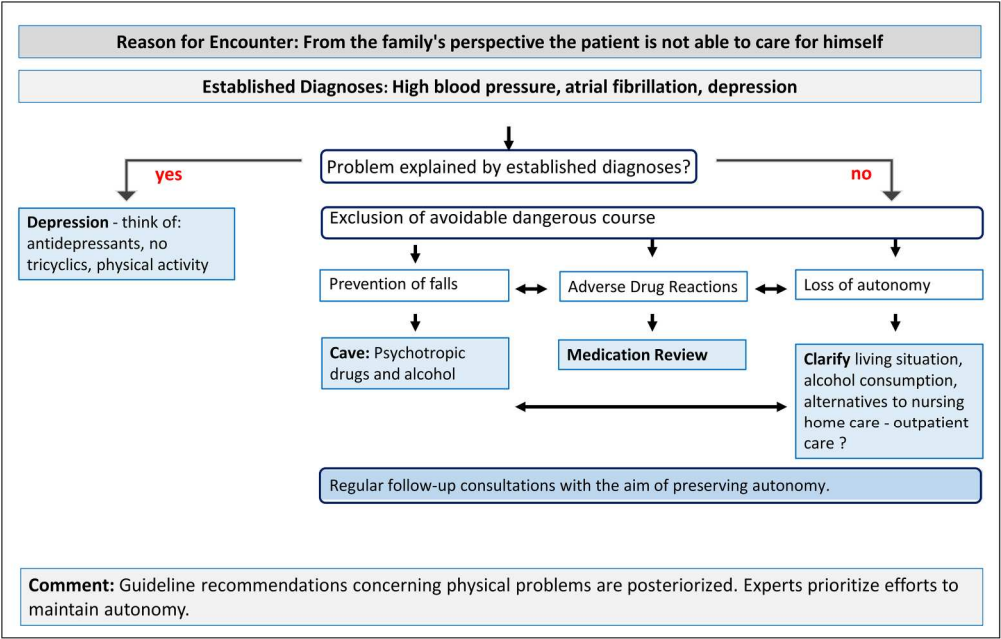
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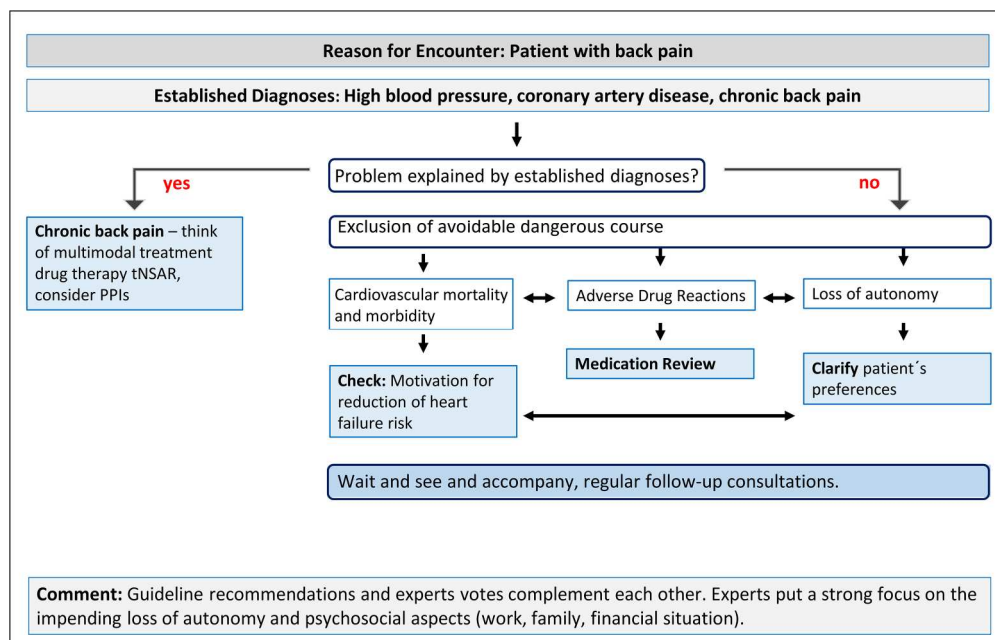
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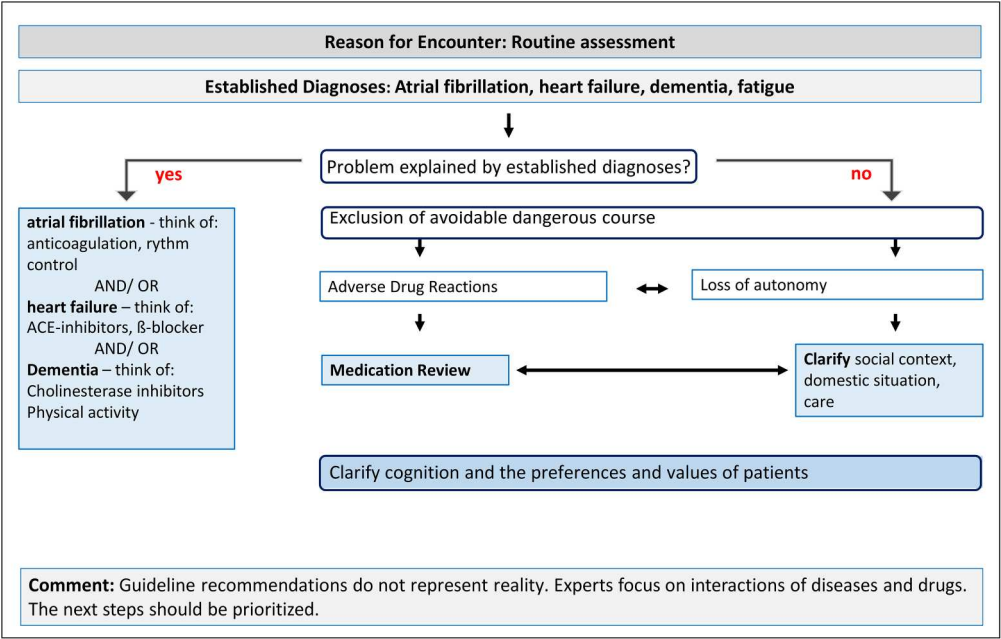
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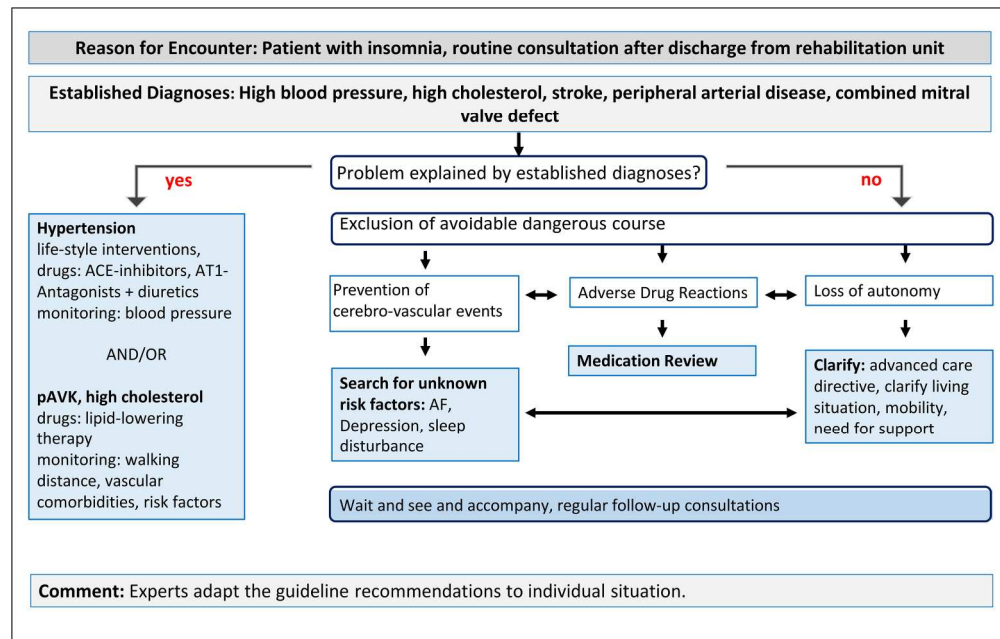
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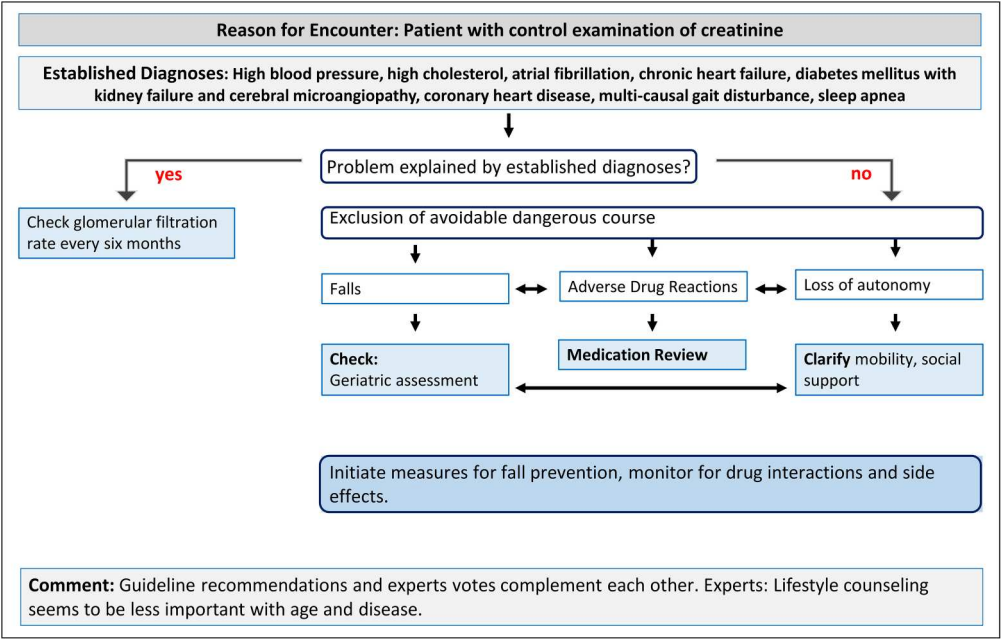
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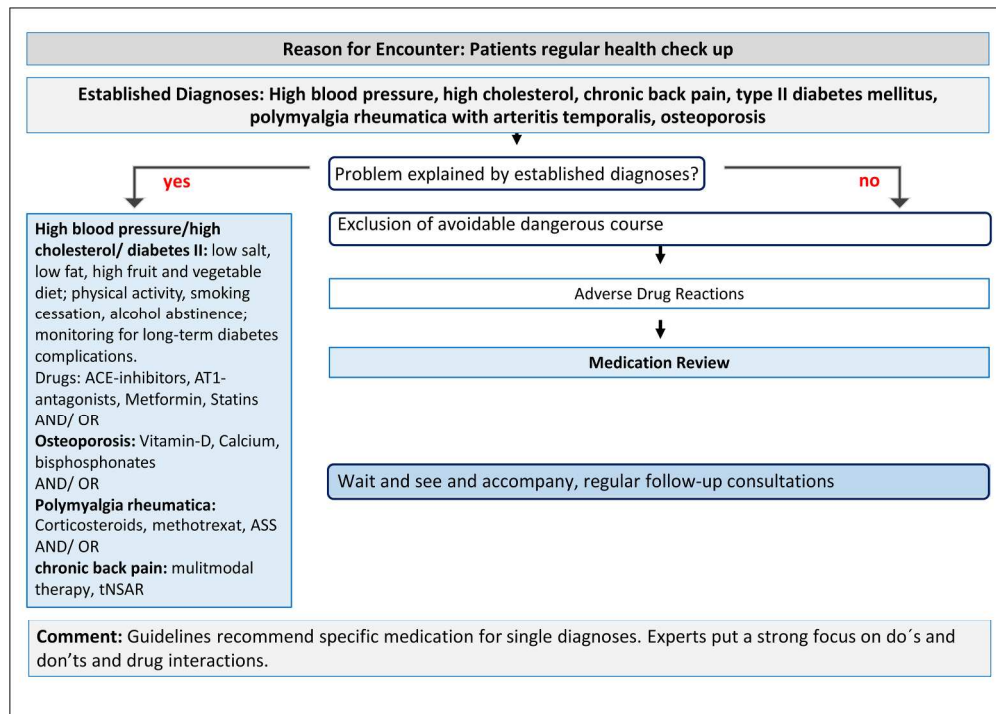


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